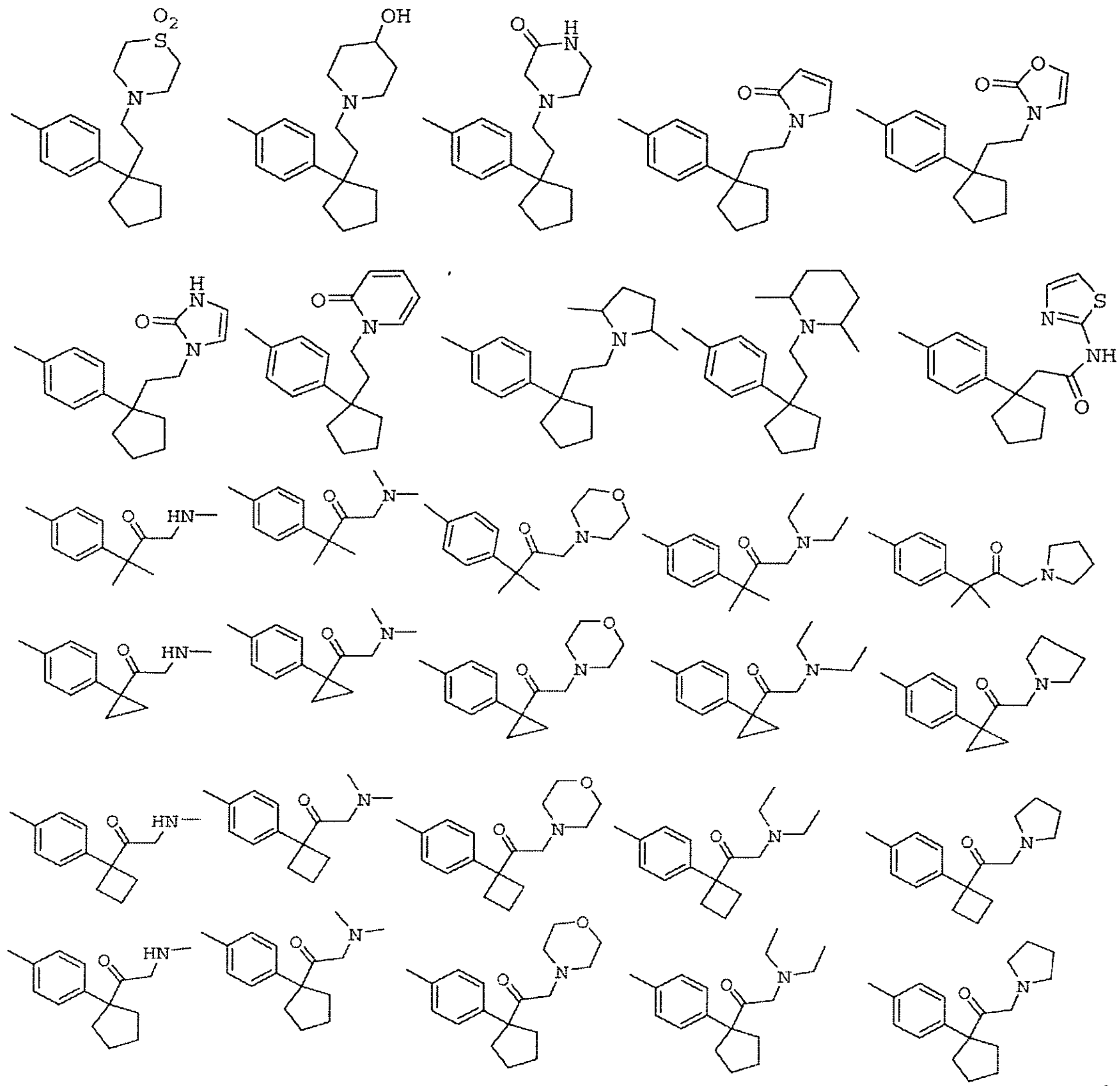


[15] In another preferred embodiment, the present invention provides a novel compound, wherein the compound is selected from the group:

1-[(6-chloro-2-naphthyl)sulfonyl]-4-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}piperazine;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-(1-pyrrolidinylmethyl)cyclopropyl]benzoyl}amino)benzamide;

N-{4-[1,1-dimethyl-2-(1-pyrrolidinyl)ethyl]phenyl}-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

N-{4-[2-(dimethylamino)-1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

N^5-{4-[2-(dimethylamino)-1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-1*H*-pyrazole-3,5-dicarboxamide;

3-cyano-*N*-{4-[2-(dimethylamino)-1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-1*H*-pyrazole-5-carboxamide;

N-{4-[2-(dimethylamino)-1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1*H*-pyrazole-5-carboxamide;

N-{4-[2-(dimethylamino)-1,1-dimethylethyl]phenyl}-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

N-(4-{1-[(dimethylamino)methyl]cyclopentyl}phenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

N-(4-{1-[(dimethylamino)methyl]cyclobutyl}phenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

N-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

1-(2,3-dihydro-1*H*-indol-6-yl)-N^5-(4-{1-[(2-oxo-1-pyrrolidinyl)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-3,5-dicarboxamide;

1-(2,3-dihydro-1*H*-indol-6-yl)-N^5-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-3,5-dicarboxamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[2-(dimethylamino)-1,1-dimethylethyl]benzoyl}amino)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(methylamino)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-(methoxymethyl)cyclopropyl]benzoyl}amino)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(dimethylamino)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(2-methyl-1-pyrrolidinyl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(2-oxo-1-pyrrolidinyl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(isopropylamino)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(cyclopropylamino)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(cyclobutylamino)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-{[4-(1-{[(2-hydroxyethyl)amino]methyl}cyclopropyl)benzoyl]amino}benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-{[4-(1-{[(2-hydroxyethyl)(methyl)amino]methyl}cyclopropyl)benzoyl]amino}benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(3-hydroxy-1-pyrrolidinyl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(4-hydroxy-1-piperidinyl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-(1-piperidinylmethyl)cyclopropyl]benzoyl}amino)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(2-oxo-1-piperidinyl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(2-oxo-1-imidazolidinyl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(2-oxo-1-pyrrolidinyl)methyl]cyclopropyl}benzyl)amino]benzamide;

2-{[4-(1-{[acetyl(methyl)amino]methyl}cyclopropyl)benzyl]amino}-5-chloro-*N*-(5-chloro-2-pyridinyl)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-({methyl[(methylamino)carbonyl]amino}methyl)cyclopropyl]benzyl}amino)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-{[4-(1-{[methyl(methylsulfonyl)amino]methyl}cyclopropyl)benzyl]amino}benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(methylsulfonyl)amino]cyclopropyl}benzyl)amino]benzamide;

2-({4-[1-(acetylamino)cyclopropyl]benzyl}amino)-5-chloro-*N*-(5-chloro-2-pyridinyl)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-{[4-(1-{[(2-hydroxyethyl)amino]methyl}cyclopropyl)benzyl]amino}benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-{[4-(1-{[(2-hydroxyethyl)(methyl)amino]methyl}cyclopropyl)benzyl]amino}benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(1,3-thiazol-2-ylamino)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[(2-methyl-1*H*-imidazol-1-yl)methyl]cyclopropyl}benzoyl)amino]benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-({4-[1-({[(methylamino)carbonyl]amino}methyl)cyclopropyl]benzoyl}amino)benzamide;

methyl [1-(4-{[(4-chloro-2-{[(5-chloro-2-pyridinyl)amino]carbonyl}phenyl)amino]carbonyl}phenyl)cyclopropyl]methylcarbamate;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-{[4-(1-{[(methylsulfonyl)amino]methyl}cyclopropyl)benzoyl]amino}benzamide;

2-({4-[1-(2-amino-2-oxoethyl)cyclopropyl]benzoyl}amino)-5-chloro-*N*-(5-chloro-2-pyridinyl)benzamide;

5-chloro-*N*-(5-chloro-2-pyridinyl)-2-[(4-{1-[2-(dimethylamino)-2-oxoethyl]cyclopropyl}benzyl)amino]benzamide;

2-({4-[1-(2-amino-2-oxoethyl)cyclopropyl]benzyl}amino)-5-chloro-*N*-(5-chloro-2-pyridinyl)benzamide;

N-{4-[1-(2-amino-2-oxoethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

N-{4-[1-(aminomethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-1*H*-1,2,3-triazole-5-carboxamide;

1-(4-methoxyphenyl)-*N*-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-1*H*-1,2,3-triazole-5-carboxamide;

1-(4-methoxyphenyl)-*N*-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-1*H*-1,2,3-triazole-5-carboxamide;

1-(4-methoxyphenyl)-N^5-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-1*H*-pyrazole-3,5-dicarboxamide;

1-(4-methoxyphenyl)-*N*5-(4-{1-[(2-oxo-1-pyrrolidinyl)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-3,5-dicarboxamide;

1-(4-methoxyphenyl)-*N*5-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-3,5-dicarboxamide;

3-cyano-1-(4-methoxyphenyl)-*N*-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-5-carboxamide;

3-cyano-1-(4-methoxyphenyl)-*N*-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-1*H*-pyrazole-5-carboxamide;

3-cyano-1-(4-methoxyphenyl)-*N*-(4-{1-[(2-oxo-1-pyrrolidinyl)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-5-carboxamide;

1-(4-methoxyphenyl)-3-(methylsulfonyl)-*N*-(4-{1-[(2-oxo-1-pyrrolidinyl)methyl]cyclopropyl}phenyl)-1*H*-pyrazole-5-carboxamide;

N-(4-{1-[(3-hydroxy-1-pyrrolidinyl)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(methylsulfonyl)-1*H*-pyrazole-5-carboxamide;

5-chloro-thiophene-2-carboxylic acid {1-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide;

5-chloro-thiophene-2-carboxylic acid {1-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {1-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {1-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoyl]-pyrrolidin-3-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide;

5-chloro-thiophene-2-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide;

2{4-[4-chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester;

2{4-[4-chloro-2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propyl alcohol;

5-chloro-*N*-(5-chloropyridin-2-yl)-2-({4-[2-(ethylamino)-1,1-dimethylethyl]benzoyl}amino)benzamide;

5-chloro-*N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)benzoyl]amino}benzamide;

5-chloro-*N*-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-morpholin-4-ylethyl)benzoyl]amino}benzamide;

2-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester;

2-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-4-methoxy-phenylcarbamoyl]-phenyl}-2-methyl-propionic acid methyl ester;

N-(5-chloropyridin-2-yl)-2-{[4-(2-hydroxy-1,1-dimethylethyl)benzoyl]amino}benzamide;

N-(5-chloropyridin-2-yl)-2-{[4-(2-hydroxy-1,1-dimethylethyl)benzoyl]amino}-5-methoxybenzamide;

N-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)benzoyl]amino}benzamide;

N-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-morpholin-4-ylethyl)benzoyl]amino}benzamide;

N-(5-chloropyridin-2-yl)-2-{[4-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)benzoyl]amino}-5-methoxybenzamide;

2-[(4-{2-[acetyl(methyl)amino]-1,1-dimethylethyl}benzoyl)amino]-*N*-(5-chloropyridin-2-yl)benzamide;

2-(4-{[2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylamino]methyl}-phenyl)-2-methyl-propionic acid methyl ester;

5-chloro-*N*-(5-chloropyridin-2-yl)-2-{[4-(2-hydroxy-1,1-dimethylethyl)benzyl]amino}benzamide;

5-chloro-N-(5-chloro-pyridin-2-yl)-2-[4-(2-dimethylamino-1,1-dimethyl-ethyl)-benzylamino]-benzamide;

N-(5-chloropyridin-2-yl)-2-({4-[1-(hydroxymethyl)cyclopropyl]benzoyl}amino)-5-methoxybenzamide;

N-(5-chloropyridin-2-yl)-5-methoxy-2-({4-[1-(pyrrolidin-1-ylmethyl)cyclopropyl]benzoyl}amino)benzamide;

N-(5-chloropyridin-2-yl)-2-({4-[1-(pyrrolidin-1-ylmethyl)cyclopropyl]benzoyl}amino)benzamide;

1-{4-[2-(5-chloro-pyridin-2-ylcarbamoyl)-phenylcarbamoyl]-phenyl}-cyclopropanecarboxylic acid methyl ester;

N-(5-chloropyridin-2-yl)-2-({4-[1-(hydroxymethyl)cyclopropyl]benzoyl}amino)benzamide;

6-chloro-3-(5-chloropyridin-2-yl)-2-[4-(1,1-dimethyl-2-morpholin-4-ylethyl)phenyl]quinazolin-4(3*H*)-one;

3-(5-chloropyridin-2-yl)-2-{4-[1-(pyrrolidin-1-ylmethyl)cyclopropyl]phenyl}quinazolin-4(3*H*)-one;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-methylamino-ethyl)-cyclopropyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-pyrrolidin-1-yl-ethyl)-cyclopropyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid [4-(1-{2-[(2-hydroxy-ethyl)-methyl-amino]-ethyl}-cyclopropyl)-phenyl]-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid (4-{1-[2-(carbamoylmethyl-methyl-amino)-ethyl]-cyclopropyl}-phenyl)-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-morpholin-4-yl-ethyl)-cyclopropyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid [4-(1-carbamoylmethyl-cyclopropyl)-phenyl]-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid [4-(1-methylcarbamoylmethyl-cyclopropyl)-phenyl]-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid [4-(1-methylcarbamoylmethyl-cyclobutyl)-phenyl]-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid [4-(1-carbamoylmethyl-cyclobutyl)-phenyl]-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-methylamino-ethyl)-cyclobutyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclobutyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-pyrrolidin-1-yl-ethyl)-cyclobutyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-morpholin-4-yl-ethyl)-cyclobutyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclopentyl]-phenyl}-amide;

5-cyano-2-(4-methoxy-phenyl)-2H-pyrazole-3-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-phenyl}-amide;

2-(4-methoxy-phenyl)-5-methyl-2H-pyrazole-3-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-phenyl}-amide;

1-(4-methoxy-phenyl)-1H-pyrazole-3,5-dicarboxylic acid 3-amide 5-({4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-phenyl}-amide);

5-methanesulfonyl-2-(4-methoxy-phenyl)-2H-pyrazole-3-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-phenyl}-amide;

3-(4-methoxy-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid {4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-phenyl}-amide;

3-(4-methoxy-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid [4-(1-carbamoylmethyl-cyclopropyl)-phenyl]-amide;

3-(4-methoxy-phenyl)-3H-[1,2,3]triazole-4-carboxylic acid [4-(1-methylcarbamoylmethyl-cyclopropyl)-phenyl]-amide;

2-[1-(4-{2-[3-(4-methoxy-phenyl)-3H-[1,2,3]triazol-4-yl]-2-oxo-ethyl}-phenyl)-cyclopropyl]-N-methyl-acetamide;

2-[1-(4-{2-[3-(4-methoxy-phenyl)-3H-[1,2,3]triazol-4-yl]-2-oxo-ethyl}-phenyl)-cyclopropyl]-acetamide;

2-[1-(4-{2-[2-(4-methoxy-phenyl)-5-trifluoromethyl-2H-pyrazol-3-yl]-2-oxo-ethyl}-phenyl)-cyclopropyl]-acetamide;

2-[1-(4-{2-[5-cyano-2-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-2-oxo-ethyl}-phenyl)-cyclopropyl]-acetamide;

2-[1-(4-{2-[5-methanesulfonyl-2-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-2-oxo-ethyl}-phenyl)-cyclopropyl]-acetamide;

2-[1-(4-{2-[5-methanesulfonyl-2-(4-methoxy-phenyl)-2H-pyrazol-3-yl]-2-oxo-ethyl}-phenyl)-cyclopropyl]-N-methyl-acetamide;

5-chloro-N-(5-chloro-2-pyridinyl)-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl] benzoyl}amino)benzamide;

N-(5-chloro-2-pyridinyl)-5-methoxy-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl] benzoyl}amino)benzamide;

N-(5-chloro-2-pyridinyl)-5-fluoro-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl] benzoyl}amino)benzamide;

N-(5-chloro-2-pyridinyl)-5-methyl-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl] benzoyl}amino)benzamide;

N-(5-chloro-2-pyridinyl)-5-methylsulfonyl-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl] benzoyl}amino)benzamide;

N-(5-chloro-2-pyridinyl)-5-cyano-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl]benzoyl}amino)benzamide;

N-(5-chloro-2-pyridinyl)-2-({4-[1-(2-dimethylamino-ethyl)cyclopropyl]benzoyl}amino)benzamide;

3-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-pyridine-2-carboxylic acid (5-chloro-pyridin-2-yl)-amide;

N-(5-chloro-pyridin-2-yl)-4-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-nicotinamide;

N-(5-chloro-pyridin-2-yl)-3-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-isonicotinamide;

N-(5-chloro-pyridin-2-yl)-2-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-nicotinamide;

5-chloro-N-(5-chloro-2-pyridinyl)-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)benzamide;

N-(5-chloro-2-pyridinyl)-5-methoxy-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)benzamide;

N-(5-chloro-2-pyridinyl)-5-fluoro-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)benzamide;

N-(5-chloro-2-pyridinyl)-5-methyl-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)benzamide;

N-(5-chloro-2-pyridinyl)-5-methylsulfonyl-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl} benzoylamino)benzamide;

N-(5-chloro-2-pyridinyl)-5-cyano-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)benzamide;

N-(5-chloro-2-pyridinyl)-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)benzamide;

3-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)-pyridine-2-carboxylic acid (5-chloro-pyridin-2-yl)-amide;

N-(5-chloro-pyridin-2-yl)-4-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)-nicotinamide;

N-(5-chloro-pyridin-2-yl)-3-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)-isonicotinamide;

N-(5-chloro-pyridin-2-yl)-2-(4-{1-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-cyclopropyl}-benzoylamino)-nicotinamide;

3-chloro-1H-indole-6-carboxylic acid {4-dimethylcarbamoyl-2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide;

3-chloro-1H-indole-6-carboxylic acid {5-dimethylcarbamoyl-2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide;

3-chloro-1H-indole-6-carboxylic acid {4-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-tetrahydro-pyran-3-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {3-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-tetrahydro-pyran-4-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {1,1-dioxo-3-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-hexahydro-1λ^6-thiopyran-4-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {1,1-dioxo-4-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-hexahydro-1λ^6-thiopyran-3-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {1-acetyl-3-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-piperidin-4-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {1-acetyl-3-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-piperidin-4-yl}-amide;

4-[(3-chloro-1H-indole-6-carbonyl)-amino]-3-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-piperidine-1-carboxylic acid methyl ester;

3-chloro-1H-indole-6-carboxylic acid {1-(2-methoxy-acetyl)-3-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-piperidin-4-yl}-amide;

5-chloro-thiophene-2-carboxylic acid {2-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-cyclopentyl}-amide;

5-chloro-thiophene-2-carboxylic acid {4-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-tetrahydro-furan-3-yl}-amide;

5-chloro-thiophene-2-carboxylic acid {1-acetyl-4-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-pyrrolidin-3-yl}-amide;

5-chloro-thiophene-2-carboxylic acid {1-cyclopropanecarbonyl-4-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-pyrrolidin-3-yl}-amide;

3-[(5-chloro-thiophene-2-carbonyl)-amino]-4-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-pyrrolidine-1-carboxylic acid methyl ester;

5-chloro-thiophene-2-carboxylic acid [4-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-1-(2-methoxy-acetyl)-pyrrolidin-3-yl]-amide;

5-chloro-thiophene-2-carboxylic acid {2-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-4-dimethylcarbamoyl-cyclopentyl}-amide;

5-chloro-thiophene-2-carboxylic acid {1-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-indan-2-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {3-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-amide;

3-chloro-1H-indole-6-carboxylic acid {3-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-7-oxa-bicyclo[2.2.1]hept-2-yl}-amide;

5-chloro-thiophene-2-carboxylic acid {2-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-4-dimethylcarbamoyl-cyclopentyl}-amide;

5-chloro-thiophene-2-carboxylic acid {8-[4-(1-dimethylaminomethyl-cyclopropyl)-benzoylamino]-1-oxa-spiro[4.4]non-7-yl}-amide;

5-chloro-thiophene-2-carboxylic acid (8-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-1-oxa-spiro[4.4]non-7-yl)-amide;

5-chloro-thiophene-2-carboxylic acid (2-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-cyclopentyl)-amide;

5-chloro-thiophene-2-carboxylic acid (2-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-4-dimethylcarbamoyl-cyclopentyl)-amide;

3-[(5-chloro-thiophene-2-carbonyl)-amino]-4-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-pyrrolidine-1-carboxylic acid methyl ester;

5-chloro-thiophene-2-carboxylic acid (4-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-tetrahydro-furan-3-yl)-amide;

3-chloro-1H-indole-6-carboxylic acid (2-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-cyclohexyl)-amide;

3-chloro-1H-indole-6-carboxylic acid (2-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-4-dimethylcarbamoyl-cyclohexyl)-amide;

4-[(3-Chloro-1H-indole-6-carbonyl)-amino]-3-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-piperidine-1-carboxylic acid methyl ester;

3-chloro-1H-indole-6-carboxylic acid (3-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-1,1-dioxo-hexahydro-1λ^6-thiopyran-4-yl)-amide;

3-chloro-1H-indole-6-carboxylic acid (4-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-1,1-dioxo-hexahydro-1λ^6-thiopyran-3-yl)-amide;

3-chloro-1H-indole-6-carboxylic acid (4-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-tetrahydro-pyran-3-yl)-amide;

3-chloro-1H-indole-6-carboxylic acid (3-{4-[1-(2-dimethylamino-ethyl)-cyclopropyl]-benzoylamino}-tetrahydro-pyran-4-yl)-amide;

(1*R*, 2*S*)-5-chloro-thiophene-2-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclopentyl}-amide;

(1*R*, 2*S*)-3-chloro-1H-indole-6-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclopentyl}-amide;

(1*R*, 2*S*)-5-chloro-thiophene-2-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-benzoylamino]-cyclohexyl}-amide; and,

Cis-3-chloro-1H-indole-6-carboxylic acid {2-[4-(1-pyrrolidin-1-ylmethyl-cyclopropyl)-phenylcarbamoyl]-cyclohexyl}-amide;

or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides novel pharmaceutical compositions, comprising: a

pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt form thereof.

In another preferred embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart.

In another preferred embodiment, the present invention provides a novel method, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

In another embodiment, the present invention provides a novel method of treating a patient in need of thromboembolic disorder treatment, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder

In another embodiment, the present invention provides a novel method, comprising: administering a compound of the present invention or a pharmaceutically acceptable salt form thereof in an amount effective to treat a thromboembolic disorder.

In another embodiment, the present invention provides a novel method for treating a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a first and second therapeutic agent, wherein the first therapeutic agent is compound of the present invention or a pharmaceutically acceptable salt thereof and the second therapeutic agent is at least one agent selected from a second factor Xa inhibitor, an anti-coagulant agent, an anti-platelet agent, a thrombin inhibiting agent, a thrombolytic agent, and a fibrinolytic agent.

In another preferred embodiment, the present invention provides a novel method, wherein the second therapeutic agent is at least one agent selected from warfarin, unfractionated heparin, low molecular weight heparin, synthetic pentasaccharide, hirudin, argatrobanas, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate,

droxicam, diclofenac, sulfinpyrazone, piroxicam, ticlopidine, clopidogrel, tirofiban, eptifibatide, abciximab, melagatran, disulfatohirudin, tissue plasminogen activator, modified tissue plasminogen activator, anistreplase, urokinase, and streptokinase.

In another preferred embodiment, the present invention provides a novel method, wherein the second therapeutic agent is at least one anti-platelet agent.

In another preferred embodiment, the present invention provides a novel method, wherein the anti-platelet agent is aspirin and clopidogrel.

In another preferred embodiment, the present invention provides a novel method, wherein the anti-platelet agent is clopidogrel.

In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,

(c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder.

In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

In another embodiment, the present invention provides a novel article of manufacture, comprising:

(a) a first container;

(b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and,

(c) a package insert stating that the pharmaceutical composition can be used in combination with a second therapeutic agent to treat a thromboembolic disorder.

In another preferred embodiment, the present invention provides a novel article of manufacture, further comprising:

(d) a second container;

wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container.

In another embodiment, the present invention provides a compound of the present invention for use in therapy.

In another embodiment, the present invention provides the use of a compound of the present invention as described above for the manufacture of a medicament for the treatment of a thromboembolic disorder.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional more preferred embodiments. It is also to be understood that each individual element of the preferred embodiments is its own independent preferred embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. All tautomers of shown or described compounds are also considered to be part of the present invention.

Preferably, the molecular weight of compounds of the present invention is less than about 500, 550, 600, 650, 700, 750, or 800 grams per mole. Preferably, the molecular weight is less than about 800 grams per mole. More preferably, the molecular weight is less than about 750 grams per mole. Even more preferably, the molecular weight is less than about 700 grams per mole.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N). The present invention, in general, does not cover groups such as N-halo, S(O)H, and SO_2H.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6

groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide ($N \rightarrow O$) derivative.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. C_{1-6} alkyl, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkyl groups. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms

attached through an oxygen bridge. C_{1-6} alkoxy, is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more unsaturated carbon-carbon bonds that may occur in any stable point along the chain, such as ethenyl and propenyl. C_{2-6} alkenyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. "Alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration and one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl. C_{2-6} Alkynyl is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3, 4, 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, 10, 11, 12, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, or unsaturated (aromatic). Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. As shown above, bridged

rings are also included in the definition of carbocycle (e.g., [2.2.2]bicyclooctane). A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a trycyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

As used herein, the term "heterocycle" or "heterocyclic group" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 1, 2, 3, or 4 ring heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., $N\rightarrow O$ and $S(O)_p$). The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic or 7, 8, 9, or 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and 1, 2, 3, or 4 heterotams independently selected from the group consisting

of N, O and S. The nitrogen atom may be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (i.e., N→O and $S(O)_p$). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Preferred bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a trycyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl,

piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected

from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodide, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicyclic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, 1990, p 1445, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian

subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. It is preferred that there presently recited compounds do not contain a N-halo, $S(O)_2H$, or $S(O)H$ group.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit factor Xa. "Therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit factor Xa. The combination of compounds is preferably a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* **1984**, *22*:27-55, occurs when the effect (in this case, inhibition of factor Xa) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antithrombotic effect, or some other beneficial effect of the combination compared with the individual components.

SYNTHESIS

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over

another in order to obtain a desired compound of the invention.

It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

The compounds of the present invention of formula I (Scheme 1) where P is not fused onto ring M can be prepared as outlined in Scheme 2 to Scheme 10 and via standard methods known to those skilled in the art.

Scheme 1

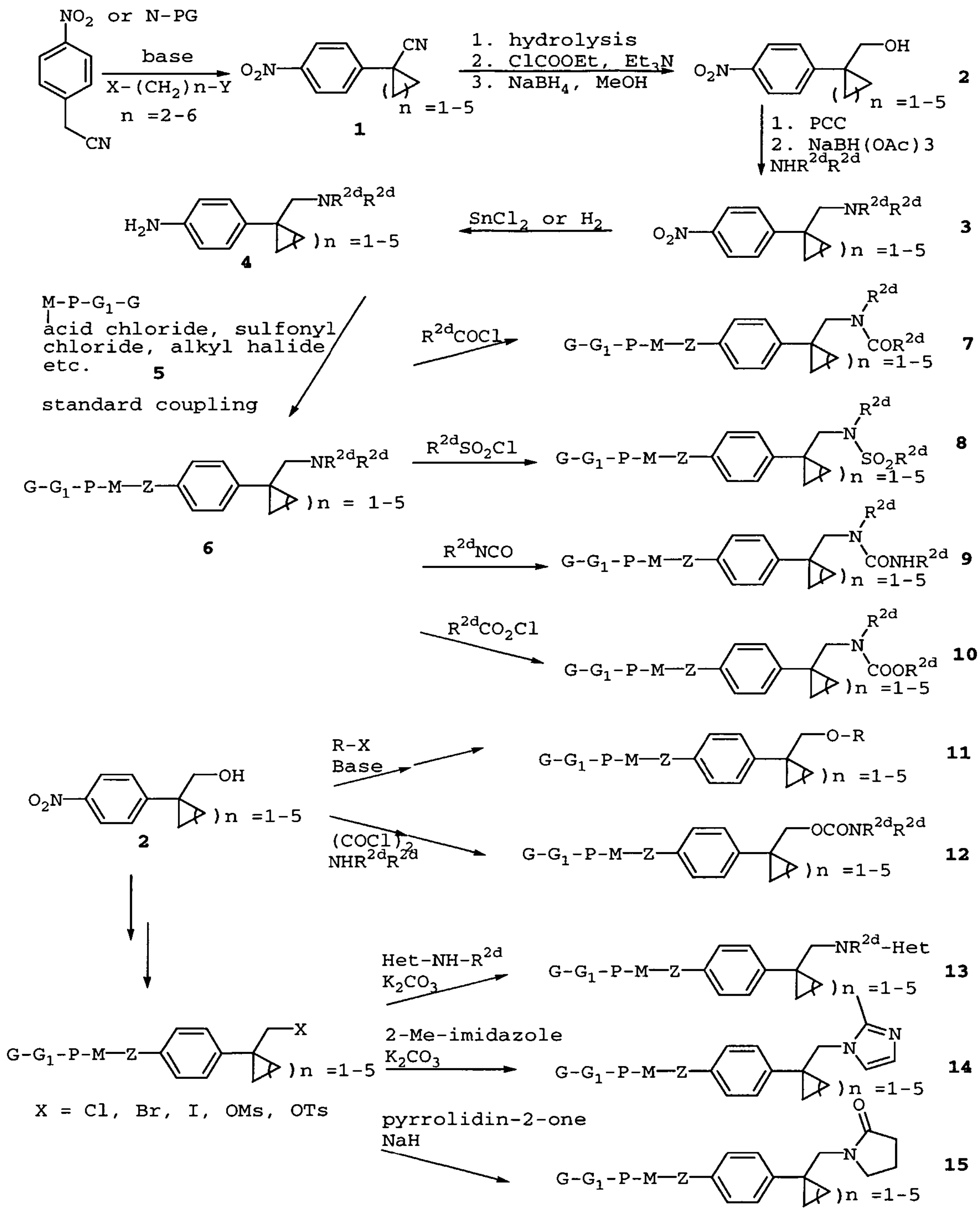
$$P_4—P—M—M_4 \equiv G\text{-}G_1—P—M—Z\text{-}A\text{-}B$$

Formula I

The compounds of the present invention of formula I where Y is C_3-C_7 cycloalkyl can be prepared as shown in Scheme 2. Commercially available 4-nitrophenylacetonitrile (or properly protected 4-aminophenylacetonitrile) can be used as the starting material. Alkylation with NaH, KtOBu, $NaNH_2$, *n*-BuLi, *s*-BuLi, NaOEt, or aq NaOH, etc. as the base, and X-$(CH_2)_n$-Y (X, Y can be Cl, Br, I, OMs or OTs, $^+S(CH_3)_2$, n = 2-6) as the alkylating reagent can afford the cycloalkyl intermediate **1**. Hydrolysis of the nitrile group, followed by reduction of the ester group can provide the alcohol **2**. Oxidation of **2**, then reductive amination with $NHR^{2d}R^{2d}$ will provide **3**. Reduction of the nitro group or deprotection of the amino group can produce the A-B precursor **4**, which can be coupled with **5** using standard

coupling conditions to provide **6**. When one of the R^{2d} groups is H, **6** can react with acid chlorides, carbamoyl chlorides, sulfonyl chlorides, and isocyanates to provide compounds of the invention with structures **7**, **8**, **9**, and **10**. Alternatively, alcohol **2** can react with alkyl halides and amines to form compounds of the invention with structures **11** and **12**. Alcohol **2** can also be transferred into a halide or its equivalents (X = Cl, Br, I, OMs, or OTs), followed by alkylation with a variety of alkylating reagents to afford compounds of the invention with structures **13**, **14**, and **15**.

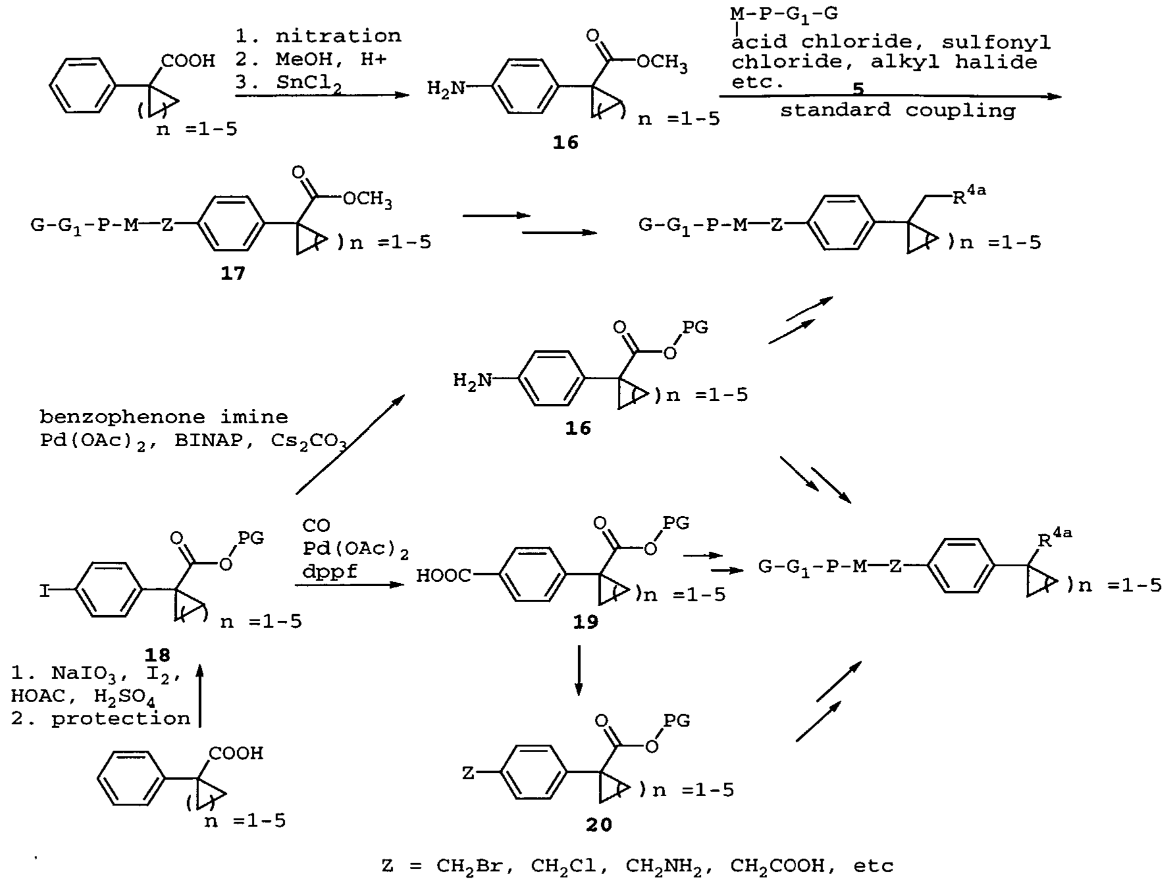
Scheme 2



Other compounds of the present invention where Y is a cycloalkyl derivative can be prepared using commercial available 1-phenylcycloalkylcarboxylic acids (or 1-phenylcycloalkylcarbonitriles) as the starting material as

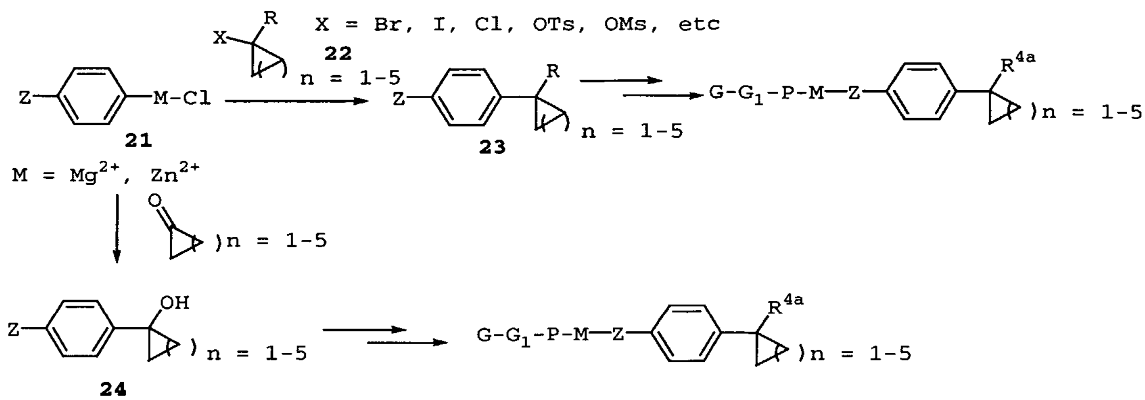
illustrated in Scheme 3. Thus, nitration, followed by reduction of the NO_2 group and protection of the acid group can provide the A-B precursor **16**, which can be coupled with **5** using standard coupling conditions to provide **17**. Alternatively, iodination will provide the desired *para*-substituted compound **18**, which can in turn be transformed to the amine **16** via Buchwald palladium-catalyzed amination (*Tetrahedron Lett.* **1997**, *38*, 6367-6370) and the acid **19** via paladium-catalyzed carboxylation (CO, Pd(OAc)2, dppf). Additional Z-linkers to the A-B intermediates can be synthesized by chemical manipulation of the amino and carboxylic acid functionality in **16** and **19**, respectively. Compound **19** can be homologated via the Arndt-Eistert methodology to afford other A-B intermediates in **20**. Alternatively, the acid functionality in **19** can be reduced to the alcohol that in turn can be converted to a variety of A-B intermediates **20** by procedures known to those skilled in the art. Further elaboration of these intermediates using the methods described above and by those skilled in the art should provide compounds of the present invention.

Scheme 3



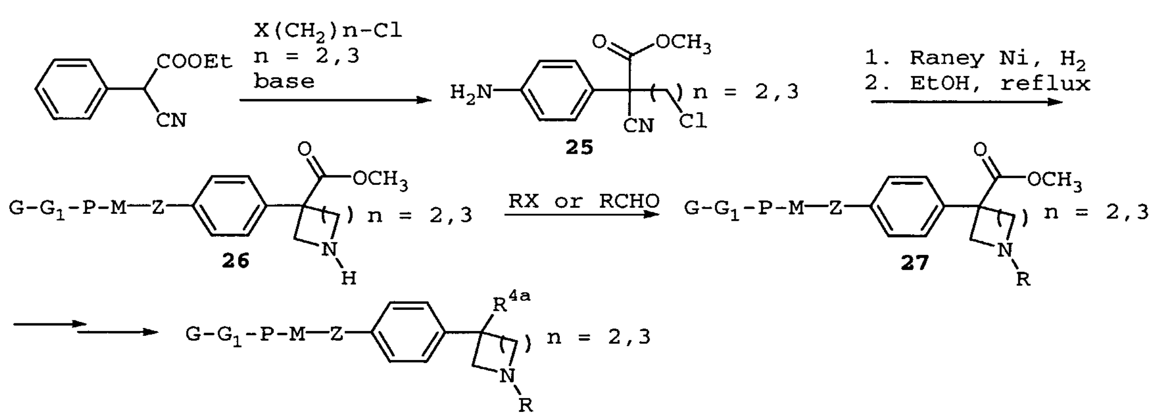
Other compounds of the present invention where Y is a cycloalkyl derivative can be prepared using organometalic reagents (Zn, Mg, etc) **21** as starting materials as shown in Scheme 4. Reaction of **21** with properly substituted cycloalkyl halides **22** (X = Cl, Br, I, OMs, OTs, etc.) using $Pd(dba)_2$/1,2-bis(diphenylphosphino)ethane (dppe) or $NiCl_2(PPh_3)_2$ as catalyst system will provide intermediate **23**. Alternatively, Grignard reaction of **21** with cycloalkyl ketones will provide intermediate **24**. Further elaboration of **23** and **24** using the methods described above and by those known in the art should provide compounds of the present invention.

Scheme 4



Compounds of formula I where Y is a pyrrolidine or piperidine derivative can be prepared as shown in Scheme 5. Thus, phenylcyanoacetate can be alkylated with X-$(CH_2)_n$-Cl (X, Y = Br, I, OMs, OTs, etc, n = 2,3) to provide the chloronitrile **25**, which can be reduced to the corresponding primary amine, followed by cyclization in refluxing EtOH to form 3-pyrrolidine or 3-piperdine derivatives **26**. Alkylation or reductive amination can provide the N-substituted intermediate **27**. Further elaboration using the methods described above and by those skilled in the art should provide compounds of the present invention.

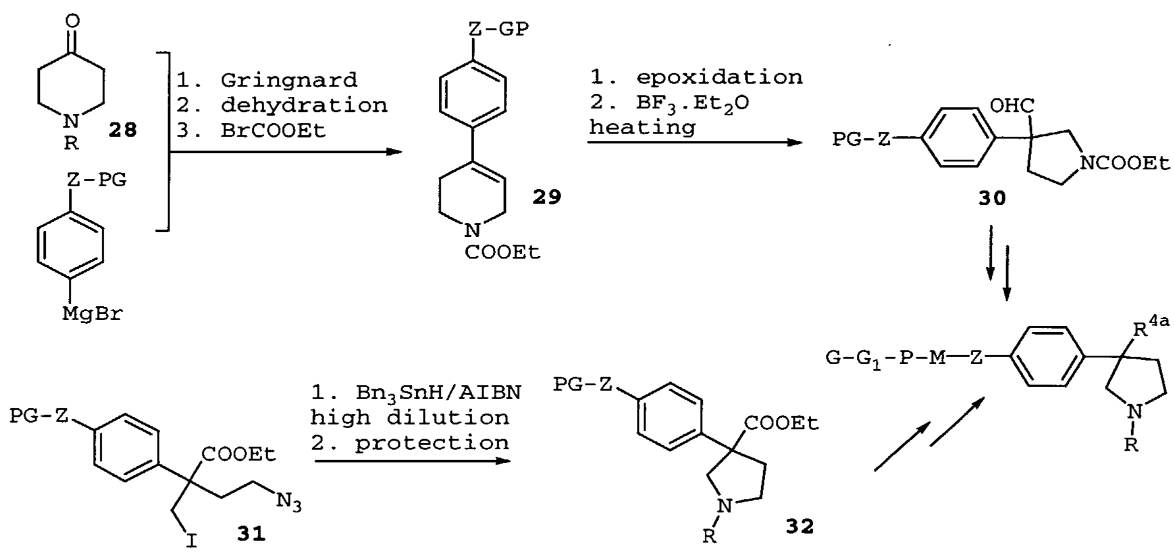
Scheme 5



Compounds of formula I where Y is a pyrrolidine derivative can also be prepared as illustrated in Scheme 6. The Grignard reaction of 1-substituted 4-piperidone **28** with

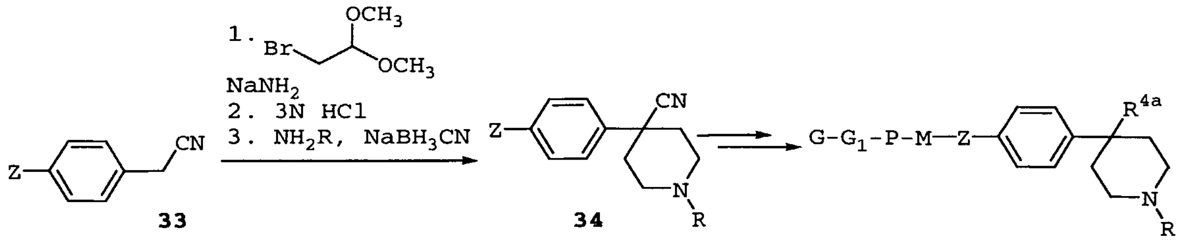
the appropriate arylmagnesium halide followed by dehydration will give tetrahydropyridine derivative **29**. Epoxidation, followed by rearrangement with heating in boron trifluroride etherate (Chem. Pharm. Bull. 28(5), 1387-1393 (1980)) will provide pyrrolidine aldehyde **30**. Alternatively, radical cyclization of alkyl azide **31** (*Tetrahedron Lett.* **1997**, *38*, 3915-1918) can provide the pyrrolidine intermediate **32**. Further elaboration of these intermediates using the methods described above and by those skilled in the art should provide compounds of the present invention.

Scheme 6



Compounds of formula I where Y is a 4-piperidine derivative can be prepared using 2-aryl acetonitriles **33** as starting materials as shown in Scheme 7. Dialkylation of **33** with bromoacetaldehyde dimethyl acetal, followed by hydrolysis of the acetals and reductive amination will give the 4-aryl-4-cyanopiperidine **34**. Further elaboration of these intermediates using the methods described above and by those skilled in the art should provide compounds of the present invention.

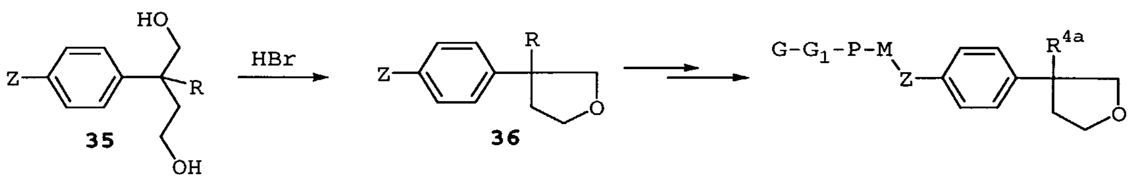
Scheme 7



33 34

Compounds of formula I where Y is a 4-tetrahydrfuran derivative can be prepared using diol **35** as the starting material as illustrated in Scheme 8. Cyclization of **35** with HBr will give the 4-aryl-4-substituted trahydrofuran **36**. Further elaboration using the methods described above and by those skilled in the art should provide compounds of the present invention.

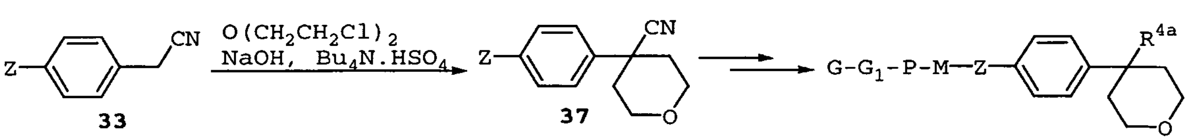
Scheme 8



35 36

Compounds of formula I where Y is a 4-tetrahydropyran derivative can be prepared using 2-aryl acetonitriles **33** as starting materials as shown in Scheme 9. Alkylation of **33** with di-2-chloroethyl ether will give the 4-aryl-4-cyanotetrahydropyran **37**. Further elaboration using the methods described above and by those skilled in the art should provide compounds of the present invention.

Scheme 9

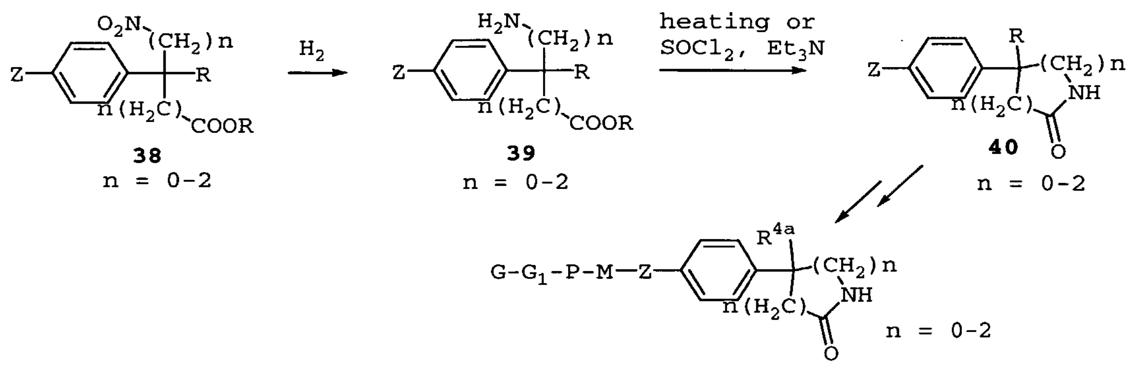


33 37

Compounds of formula I where Y is a lactam derivative can be prepared using intermediate **38** as the starting

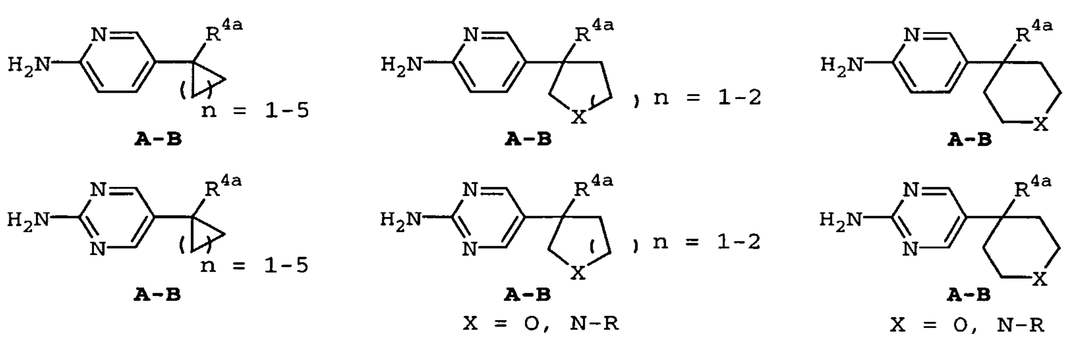
material as shown in Scheme 10. Reduction of NO_2 group or nitrile group will provide the primary amine **39**, which can be coupled intramolecularly with the acid or ester to form the lactam **40**. Further elaboration using the methods described above and by those skilled in the art should provide compounds of the present invention.

Scheme 10



Aminopyridyl and aminopyrimidyl A-B analogs (see structures in Scheme 11) can be prepared using routes similar to those of Schemes 2-10 and by those skilled in the art. These intermediates can then be further manipulated to compounds of this invention with formula I via procedures previously described.

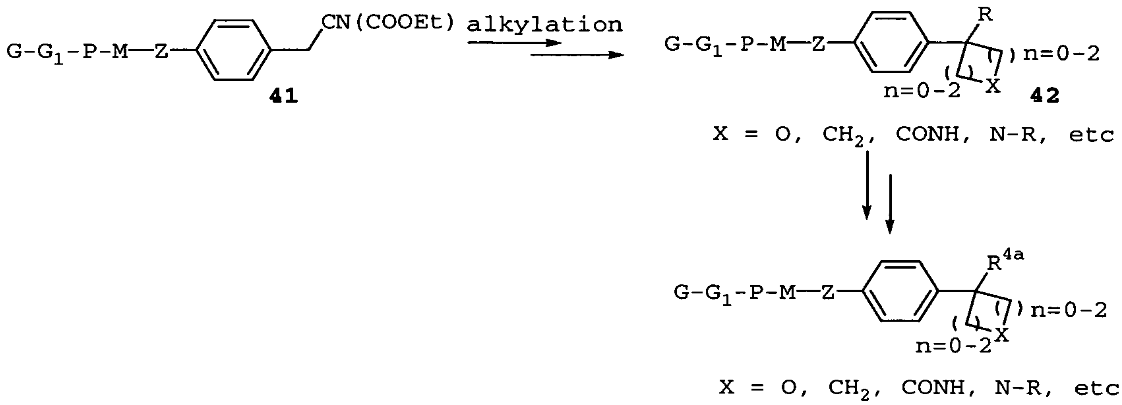
Scheme 11



Compounds of formula I (Scheme 1) where P is fused onto ring M can be prepared as outlined in Schemes 12 and 13, and via standard methods known to those skilled in the

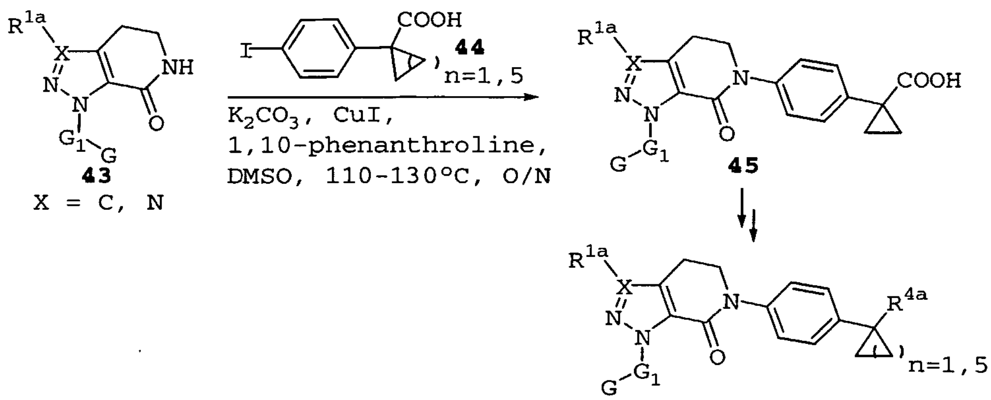
art. The ester or nitrile intermediates **41** illustrated in these Scheme 12 can be subjected to alkylation conditions, followed by other manipulations as described in Schemes 2-10. Further elaboration of intermediates **42** to incorporate the appropriate R^{4a} groups using the methods described above and by those skilled in the art should provide compounds of the present invention.

Scheme 12



Scheme 13 illustrates the synthesis of compounds of formula I (Scheme 1) when P-M moiety **43** is a bicyclic lactam moiety. Thus, the iodo A-B intermediate **44** will react with **43** under Buchwald modified Ullman reaction (*J. Am. Chem. Soc.* **2001**, *123*, 7727) using CuI and 1,2-cyclohexyldiamine or 1,10-phenanthroline as the catalyst system to provide **45** in high yields. Further elaboration of **45** to incorporate the appropriate R^{4a} groups art should provide compounds of the present invention by using the methods described above and by those skilled in the art.

Scheme 13



Schemes 2-13 describe how to make the A-B moieties of the present invention and how to couple them to prepare compounds of the present invention. Schemes 2-13 describe A-B wherein B is Y-R^{4a} and Y is a cycloalkyl or heterocyclyl. Compounds of the present invention wherein Y is CY^1Y^2 can be made analogously to the cycloalkyl/heterocyclyl compounds of Schemes 2-13. For example, in Scheme 2, instead of intermediate **1** being a cycloalkyl intermediate, it can be Y^1Y^2 disubstituted intermediate. This intermediate could be made by a number of methods including di-substituting the starting 4-nitrophenylacetonitrile by reaction with a base and a Y^1-leaving group and a Y^2-leaving group. One of ordinary skill in the art would recognize that other routes to the Y^1Y^2 disubstituted intermediate are available. The remainder of the chemistry shown in Scheme 3 will then follow.

In Scheme 3, instead of use the starting 1-phenylcycloalkylcarboxylic acids or 1-phenylcycloalkylcarbonitriles of Scheme 3, one could use the corresponding Y^1Y^2 disubstituted intermediates. Just like in Scheme 2, these intermediates could be prepared by di-substituting a phenylcarboxylic acid or phenylcarbonitrile. One of ordinary skill in the art would recognize that other routes to these types of Y^1Y^2

disubstituted intermediate are also available. The remainder of the chemistry shown in Scheme 3 will then follow.

The compounds of this invention and the intermediates described above wherein the B group contains an oxidizable group can be oxidized, e.g., N to N-oxide.

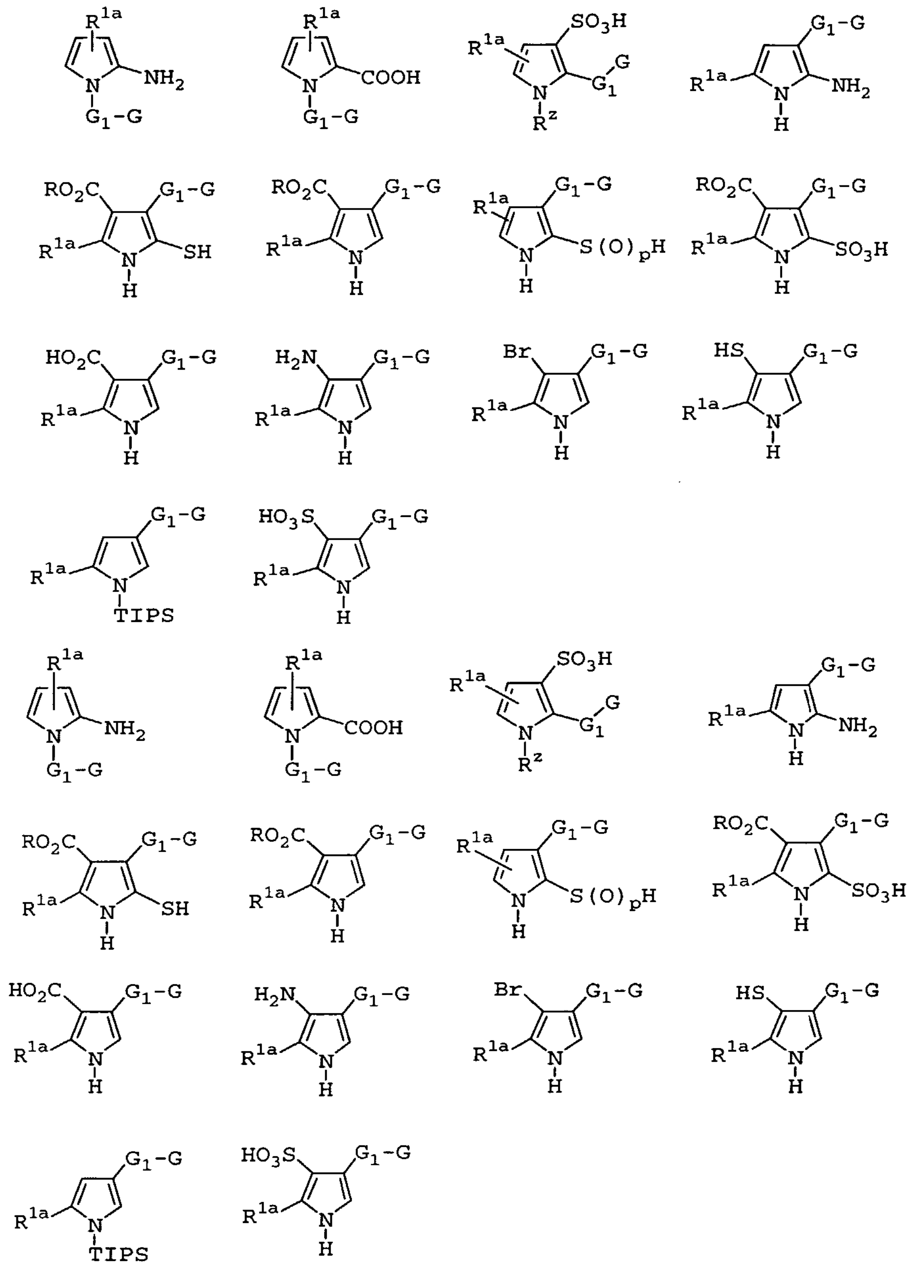
In the above Schemes, the Z group may or may not be present depending on how the A-B group is coupled. The coupling portion of the A-B group could (a) be displaced by the incoming Z or M group, (b) become the Z group, or (c) be incorporated into ring M.

The remaining portions of the compounds of the present invention, G-G_1-P-M-Z, G-G_1-M-P-Z, G-G_1-P-M, G-G_1-M-P, G-G_1-M-Z, and G-G_1-M, can be prepared using methods known to those of ordinary skill in the art. All of the following patents and publications are incorporated herein by reference. For compounds wherein ring P is absent and ring M is a 5-, 6-, or 7-membered ring, one of ordinary skill in the art can look to US 5,939,418, US 5,925,635, US 6,057,342, US 6,187,797, US 6,020,357, US 6,060,491, US 5,998,424, US 6,191,159, WO98/57951, WO99/32454, WO00/039108, WO00/059902, WO01/32628, WO01/005785, WO02/00651, WO02/102380, and WO02/00647 for starting materials and intermediates to which the present B and/or A-B groups can be coupled. For compounds wherein ring P is fused to ring M (i.e., a bicyclic moiety is present), one of ordinary skill in the art can look to WO00/39131, WO02/094197, USSN 10/104,467, USSN 10/105,477, and WO02/00655 for starting materials and intermediates to which the present B and/or A-B groups can be coupled.

For compounds wherein G is a ring substituted with a basic moiety, one of ordinary skill in the art can look to US 5,939,418, US 5,925,635, US 6,057,342, US 6,187,797, US 6,020,357, US 6,060,491, US 6,191,159, WO98/57951, WO99/32454 WO00/059902, WO01/32628, WO00/39131, WO02/00651, WO02/102380, WO02/094197, USSN 10/104,467, and USSN

10/105,477 for starting materials and intermediates to form the present G-G_1-P-M-Z, G-G_1-M-P-Z, G-G_1-P-M-Z-A, and/or G-G_1-M-P-Z-A groups to which the present B and/or A-B groups can be coupled. For compounds wherein G is a ring substituted with a non-basic group, one of ordinary skill in the art can look to US 5,998,424, WO00/39131, WO00/059902, WO01/32628, WO02/00651, WO02/102380, WO02/094197, USSN 10/104,467, and USSN 10/105,477 for starting materials and intermediates to form the present G-G_1-P-M-Z, G-G_1-M-P-Z, G-G_1-P-M-Z-A, and/or G-G_1-M-P-Z-A groups to which the present B and/or A-B groups can be coupled. For compounds wherein G is a bicyclic moiety, one of ordinary skill in the art can look to WO98/57951 WO00/039108, WO00/39131, WO02/00651, WO02/102380, WO02/094197, USSN 10/104,467, and USSN 10/105,477 for starting materials and intermediates to form the present G-G_1-P-M-Z, G-G_1-M-P-Z, G-G_1-P-M-Z-A, and/or G-G_1-M-P-Z-A groups to which the present B and/or A-B groups can be coupled. For compounds wherein A is an indoline or similar bicycle, one of ordinary skill in the art can look to WO01/005785 for starting materials and intermediates to which the present B group can be coupled or from which the present A-B groups can be formed. Scheme 14 illustrates some of the numerous pyrrole intermediates that can be used to prepare compounds of the present invention (R^z is the point of attachment for Z-A-B and can be H, a protecting group, a group modifiable to Z or Z-A, Z, Z-A, or A). These intermediates are described in the above-noted patents and publications.

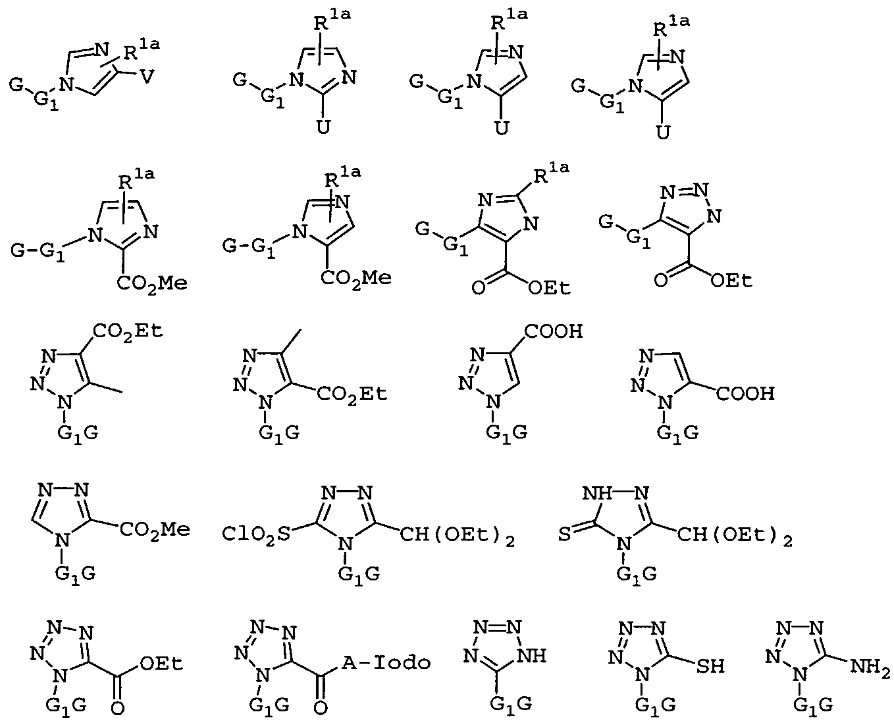
Scheme 14



Scheme 15 illustrates some of the numerous imidazole, triazole, and tetrazole intermediates that can be used to prepare compounds of the present invention. These intermediates are described in the above-noted patents and publications. In Scheme 15, V is nitro, amino, thio, hydroxy, sulfonic acid, sulfonic ester, sulfonyl chloride, ester, acid, or halide. In Scheme 15, U is aldehyde,

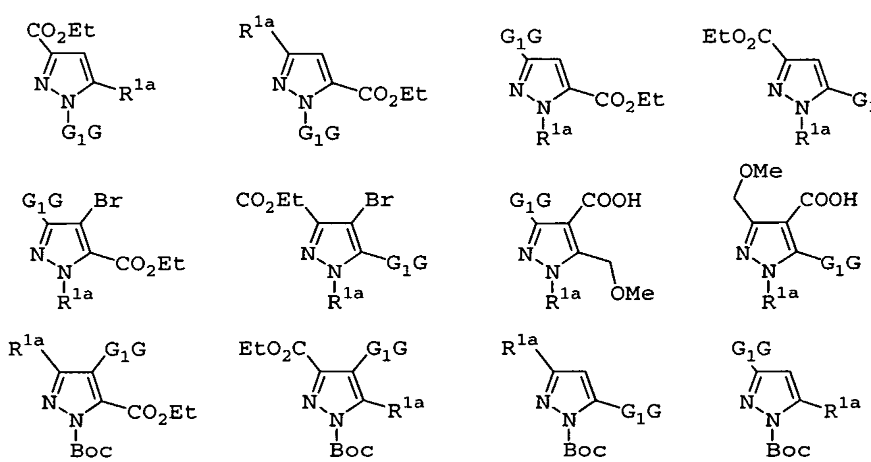
ester, acid, amide, amino, thiol, hydroxy, sulfonic acid, sulfonic ester, sulfonyl chloride, or methylene halide.

Scheme 15



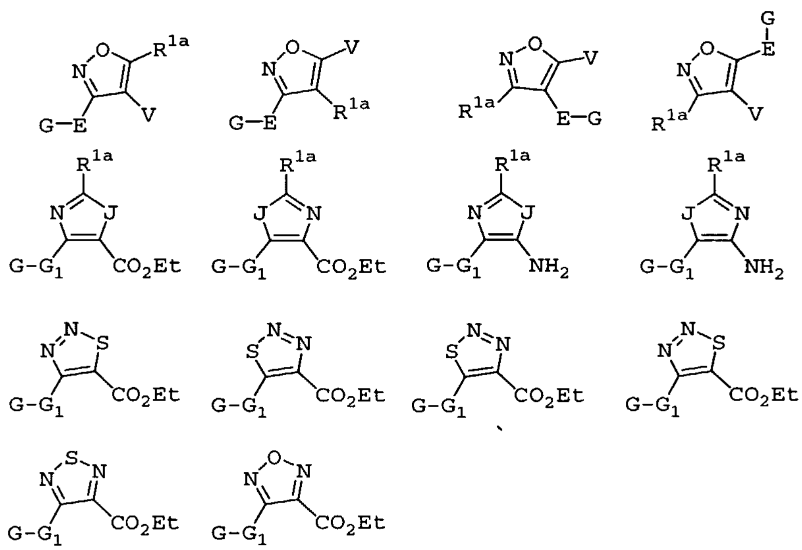
Scheme 16 shows some of the numerous pyrazole intermediates that can be used to prepare compounds of the present invention. These intermediates are described in the above-noted patents and publications.

Scheme 16



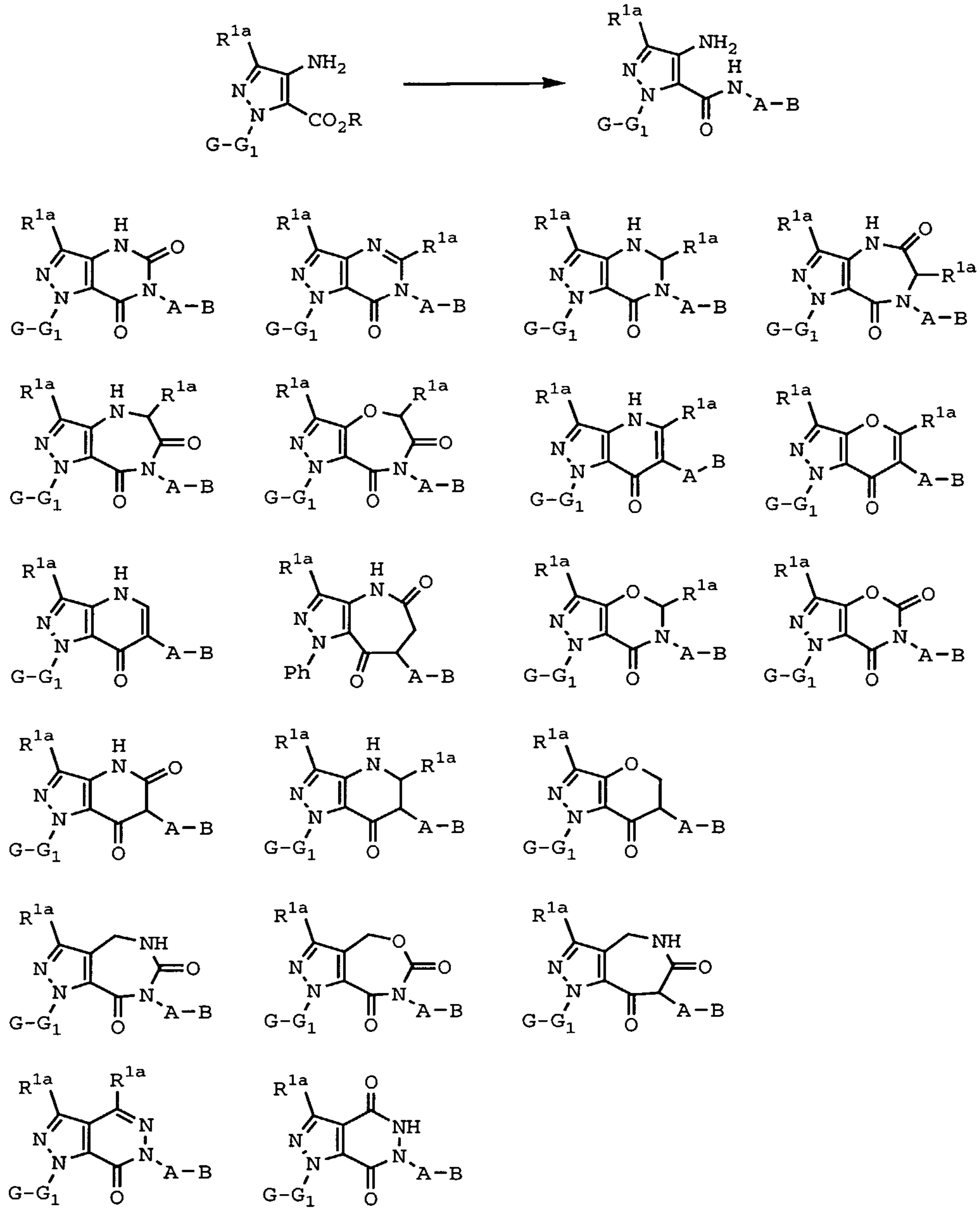
Scheme 17 depicts some of the numerous oxazole, thiazole, isoxazole, oxadiazole, and thiadiazole intermediates that can be used to prepare compounds of the present invention. These intermediates are described in the above-noted patents and publications. In Scheme 17, V is nitro, amino, ester, or acid.

Scheme 17



Scheme 18 illustrates two intermediates useful for making a compound of the present invention wherein ring P is fused to ring M. Scheme 18 also illustrates a number of bicyclic compounds that can be made from these intermediates or derivatives thereof. These intermediates and their modification are described in the above-noted patents and publications.

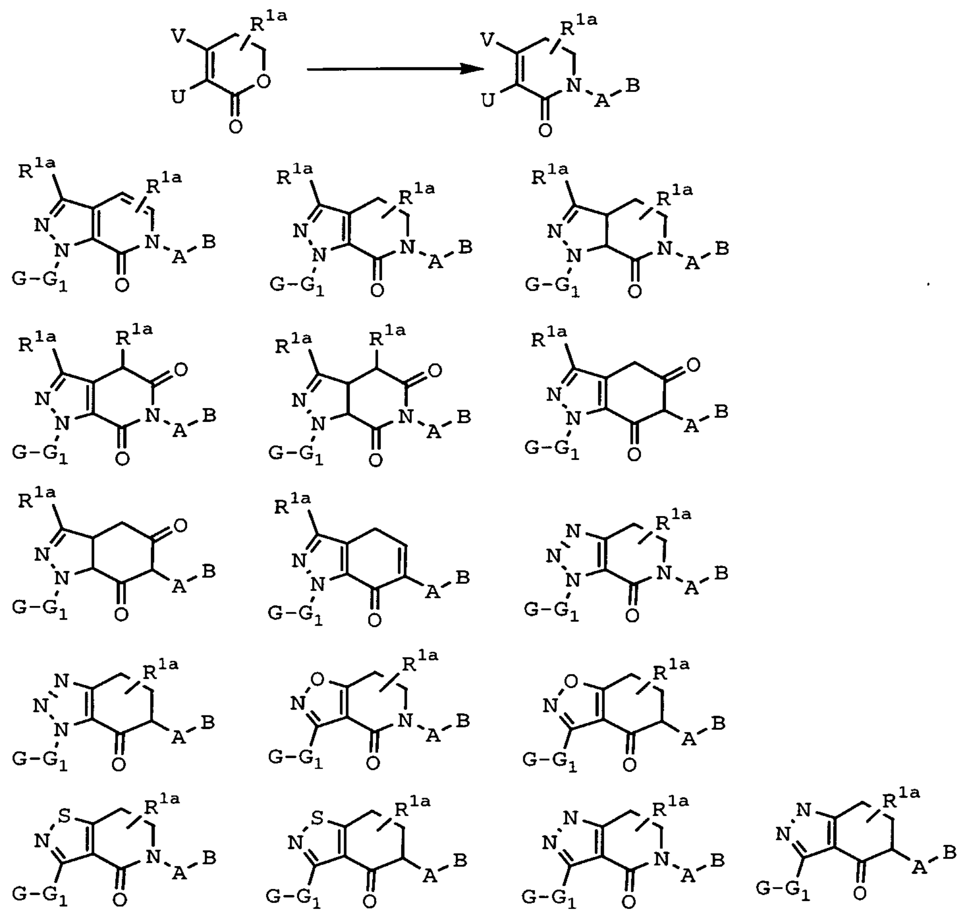
Scheme 18



Scheme 19 depicts another intermediate useful for making a compound of the present invention wherein ring P is fused to ring M. Scheme 19 also illustrates a number of bicyclic compounds that can be made from this intermediate or derivatives thereof (e.g., the corresponding cyclohexenone). In Scheme 19, U is OH or morpholine and V is H or C(O)R^{1a}. This intermediate, derivatives thereof,

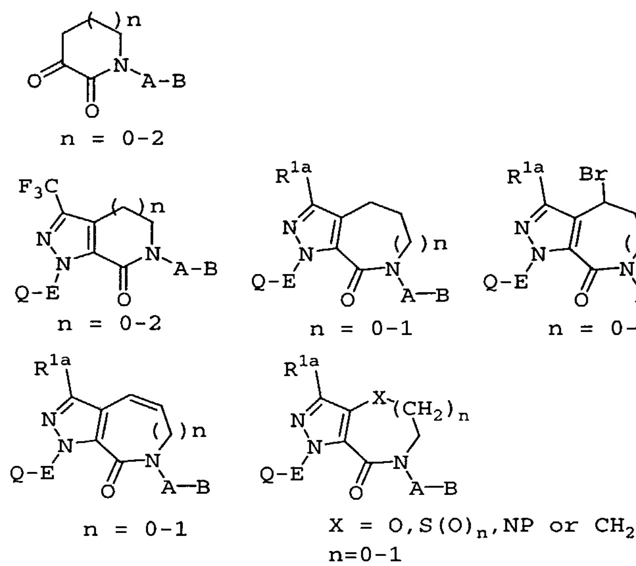
and their modification are described in the above-noted patents and publications.

Scheme 19



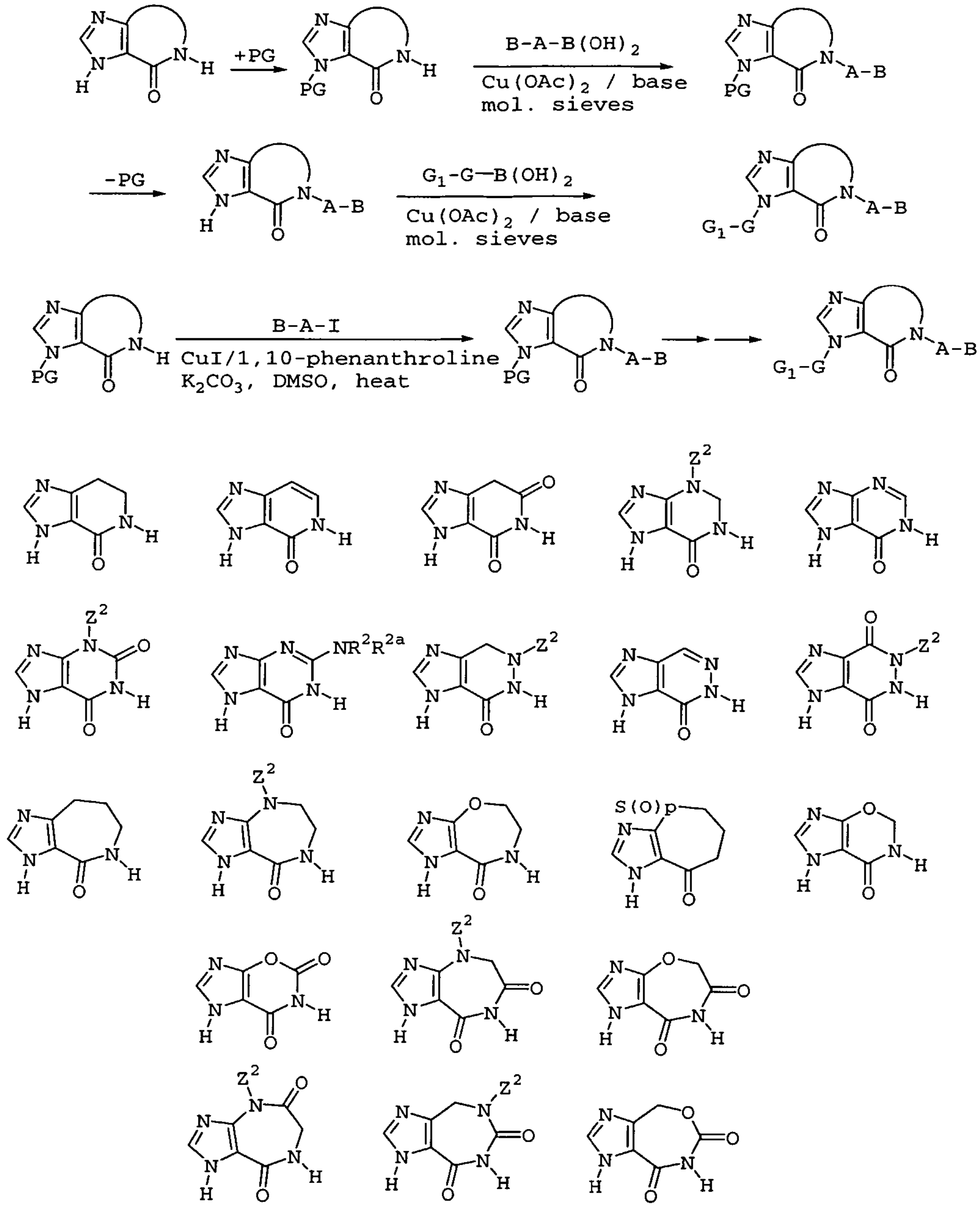
Scheme 20 shows another intermediate useful for making a compound of the present invention wherein ring P is fused to ring M. Scheme 20 also illustrates a number of bicyclic compounds that can be made from this intermediate or derivatives thereof. This intermediate, derivatives thereof, and their modification are described in the above-noted patents and publications.

Scheme 20



Scheme 21 illustrates a number of other bicyclic rings that are considered to be part of the present bicyclic group, rings P-M. Scheme 21 also describes a method of converting the shown rings to compounds of the present invention. As one of ordinary skill in the art would recognize, this method would be applicable to other heterobicyclics not shown.

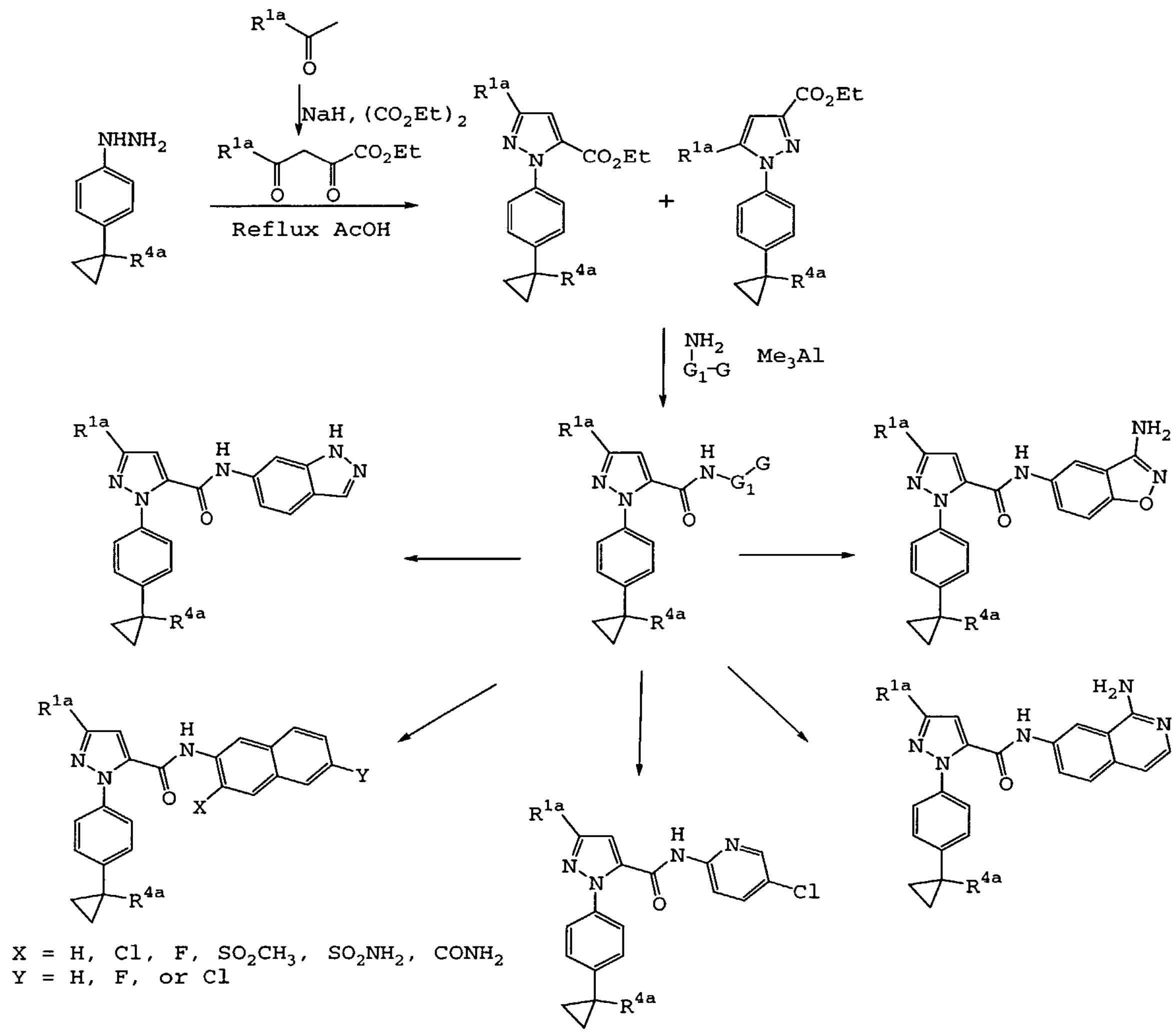
Scheme 21



Other useful pyrazole intermediates wherein G_1 is an amide are exemplified in Scheme 22. Compounds of the present invention wherein the G_1 group is other than an amide can be easily manipulated to other linker functionalities according to the methodologies known in the art, including the methodologies outlined in WO98/28269 and

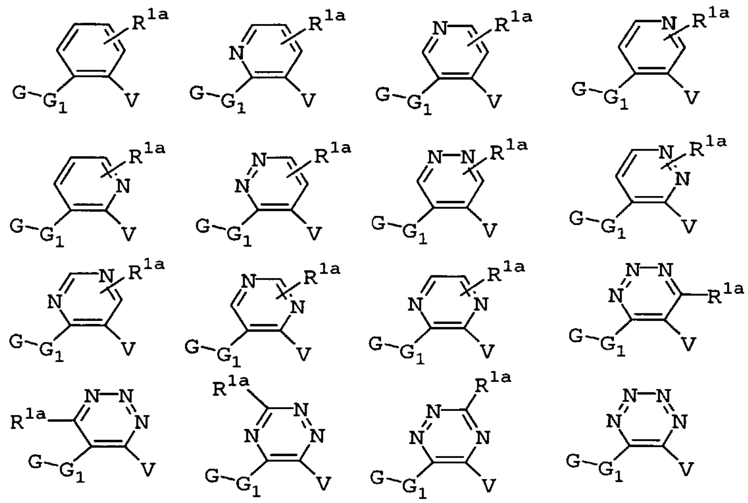
WO98/28282, the contents of both are incorporated herein by reference.

Scheme 22



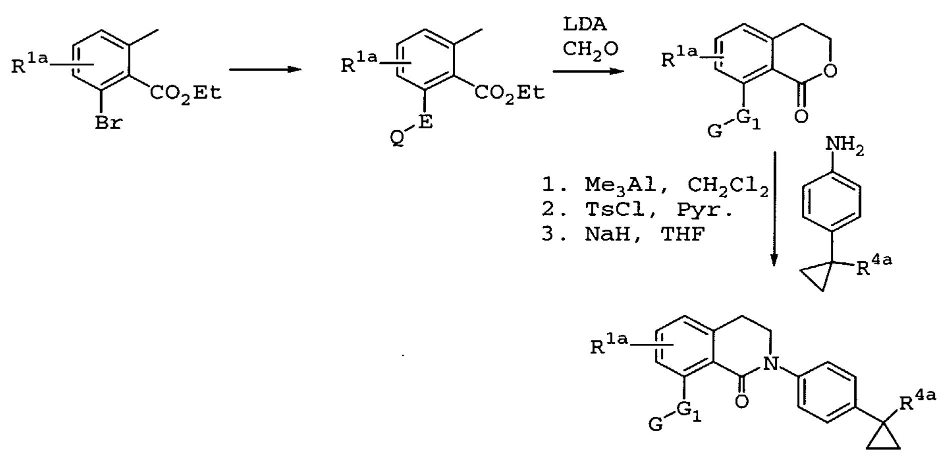
Scheme 23 depicts some of the numerous 6-membered aromatic ring intermediates that can be used to prepare compounds of the present invention. These intermediates are described in the above-noted patents and publications. In Scheme 23, V is nitro, protected sulfonamide, or ester group and is a precursor of group Z of the present invention.

Scheme 23



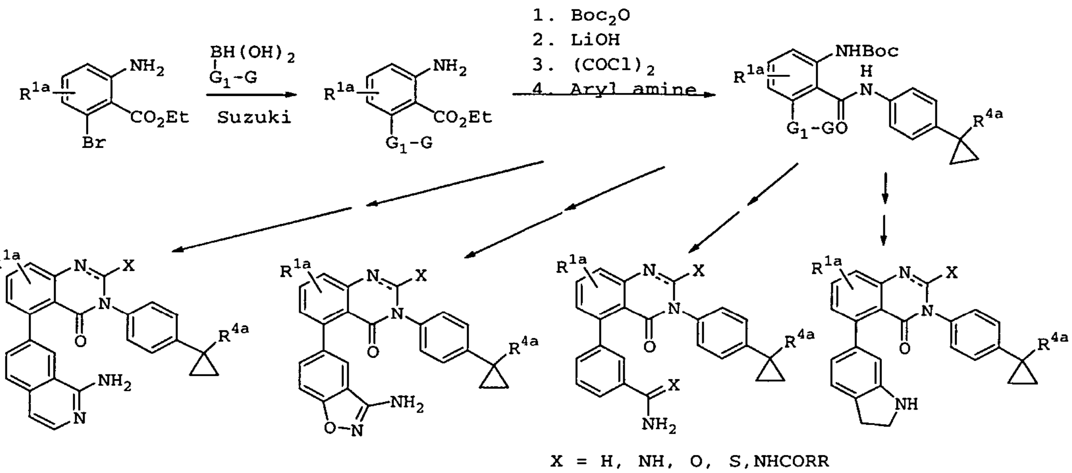
Benzo fused dihydro-pyridone intermediates of the present invention can be prepared from readily available starting materials as shown in Scheme 24.

Scheme 24

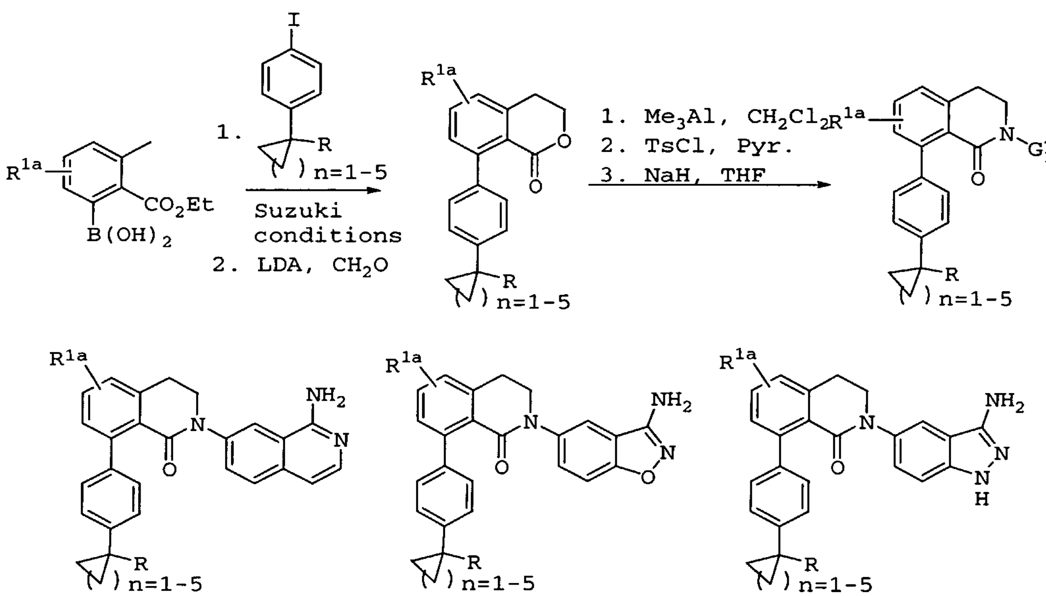


Other benzo-bicyclics can also be obtained as shown in Schemes 25 and 26.

Scheme 25

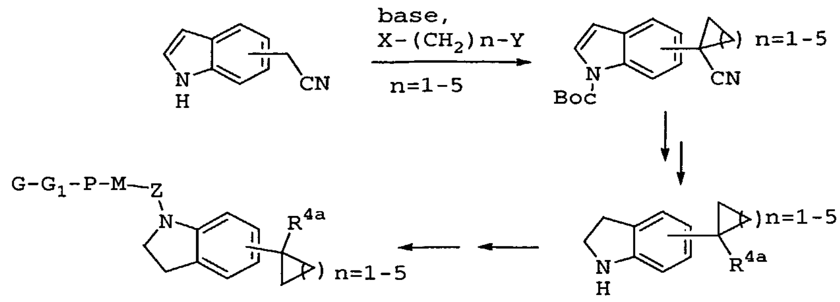


Scheme 26



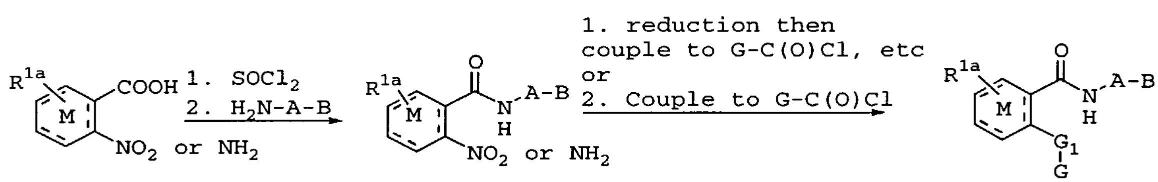
Intermediates A-B of the present invention wherein A is indoline can be prepared as shown in scheme 27. This type of intermediate can then be attached to the remainder of the desired compound as described previously. Alternatively, the indoline can be attached to the other half of the desired compound prior to formation of the carbocyclic or heterocyclic ring.

Scheme 27



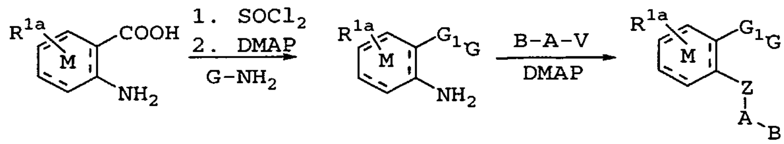
Compounds of the present invention wherein ring P is absent and ring M is a six-membered ring can be obtained as shown in scheme 28. These types of compounds can be obtained from commercially available anthranilic acids or their anthranilates. Anthranilic acids or their nitro precursors can be coupled with a suitable B-A-NH_2 in presence of a base such as triethyl amine, pyridine, or DMAP. Subsequent coupling with an appropriate acid chloride or aniline or aminopyridyl should afford compounds of the present invention.

Scheme 28



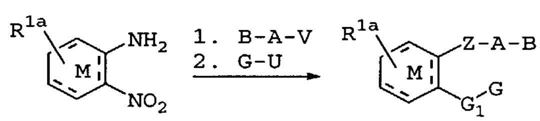
In an analogous fashion the anthranilates can be coupled with a suitable amine, aniline, or aminopyrimidyl to afford the corresponding benzamide. The benzamides can then be coupled with an appropriate B-A-V (wherein V is a acid chloride derivative, an alkyl halide, or a sulfonyl chloride) to afford additional compounds of the present invention (see scheme 29).

Scheme 29



Commercially available ring M derivatives bearing a nitro and amino functionality can also be derivatized as shown above to afford bisamide analogs. In this case, coupling of the aniline with B-A-V (wherein V is an acid chloride, a sulfonyl chloride, or an alkylhalide) affords an intermediate that can be subjected to treatment with an appropriate G-U (wherein U is either an acid chloride or an alkyl halide) in presence of a suitable base such as DMAP. It should be noted that the order of addition of B-A-V and G-U can be reversed to obtain other compounds of the present invention (see scheme 30).

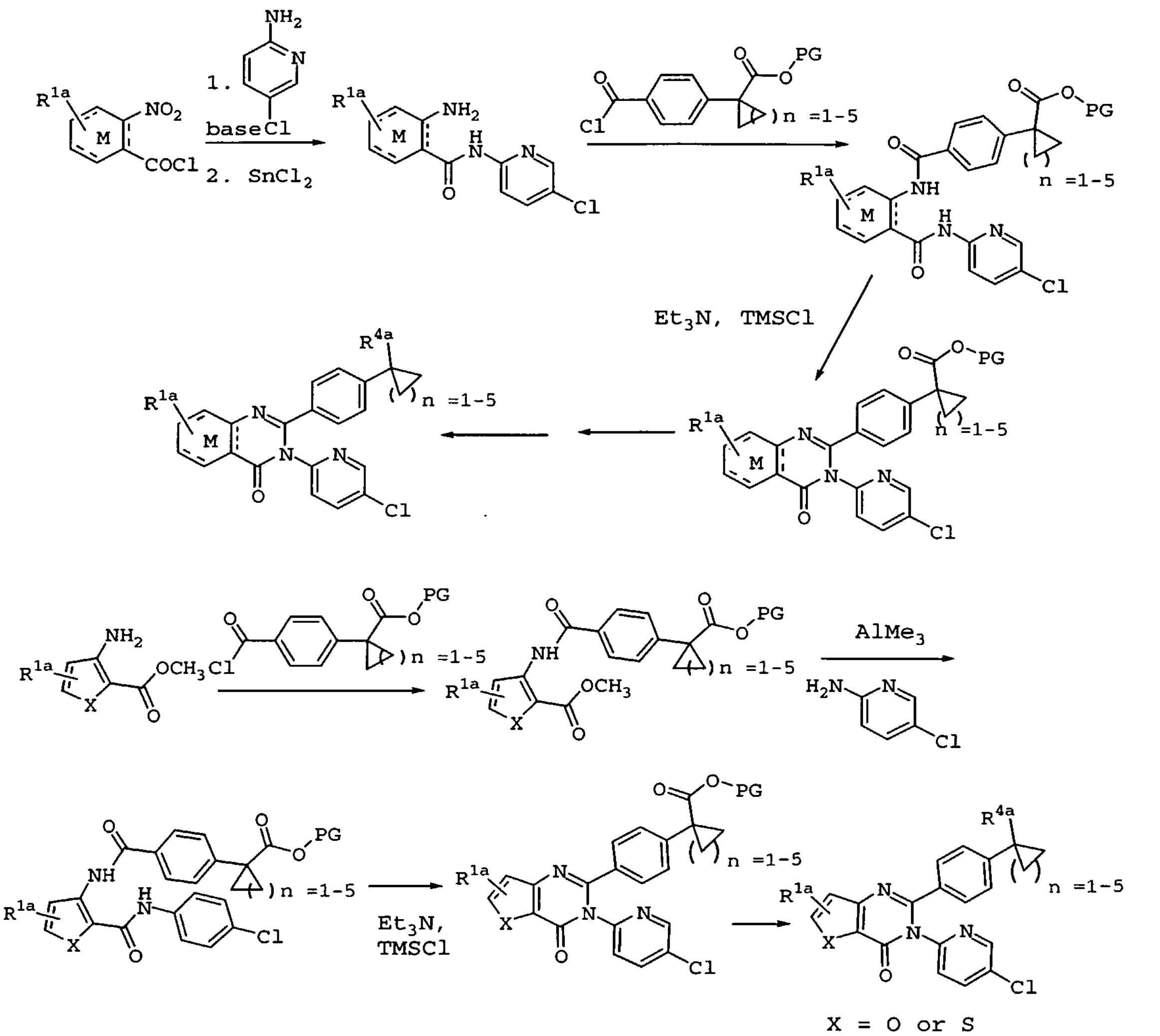
Scheme 30



It should be noted that the syntheses shown above could be modified to use coupling intermediates such as Iodo-A-V, wherein V is an acid chloride, amino, alkylhalide, or sulfonyl chloride. These in turn could be coupled to a G-U group. The iodo intermediate could then be subjected to Ullman or Buchwald coupling as described previously to afford compounds of the present invention. The iodo intermediate could also be converted to an amine via standard Buchwald conditions to afford the corresponding anilino intermediate. This in turn could be coupled as previously described to afford compounds of the present invention.

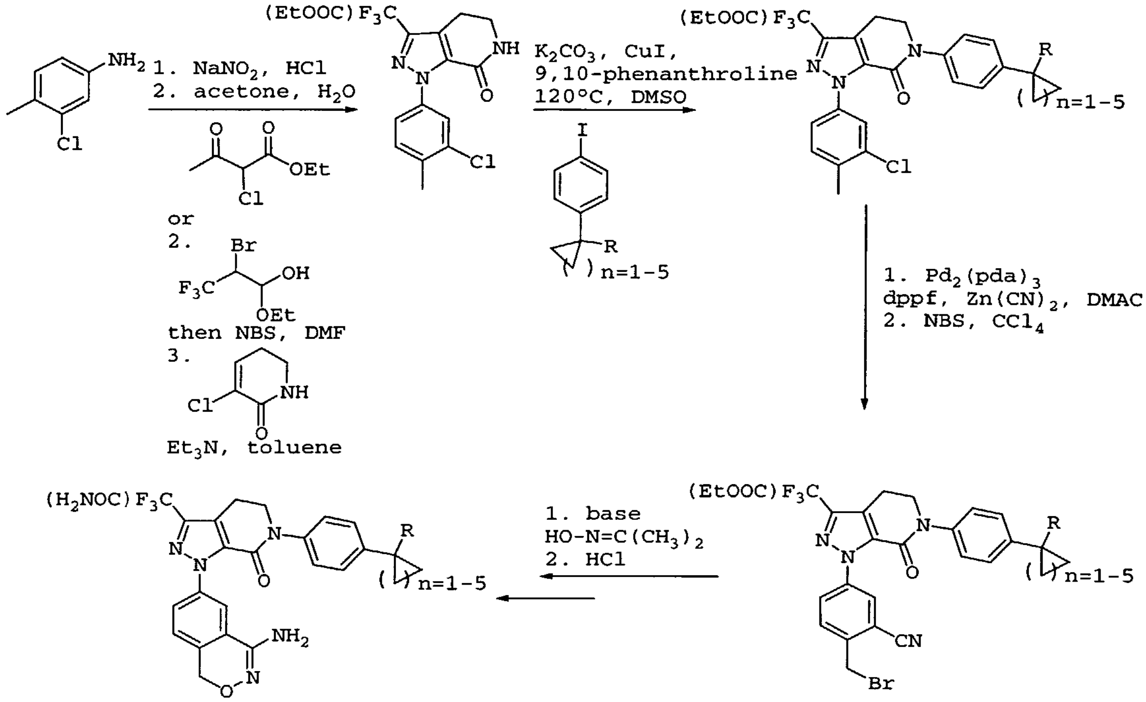
The syntheses of bisamide compounds shown in Schemes 28-30 can also be applied to the syntheses of compounds with ring M as a 5-membered heterocycle. The bisamides can also be further converted into bicyclic pyrimidin-4-ones under acidic conditions as shown in Scheme 31.

Scheme 31



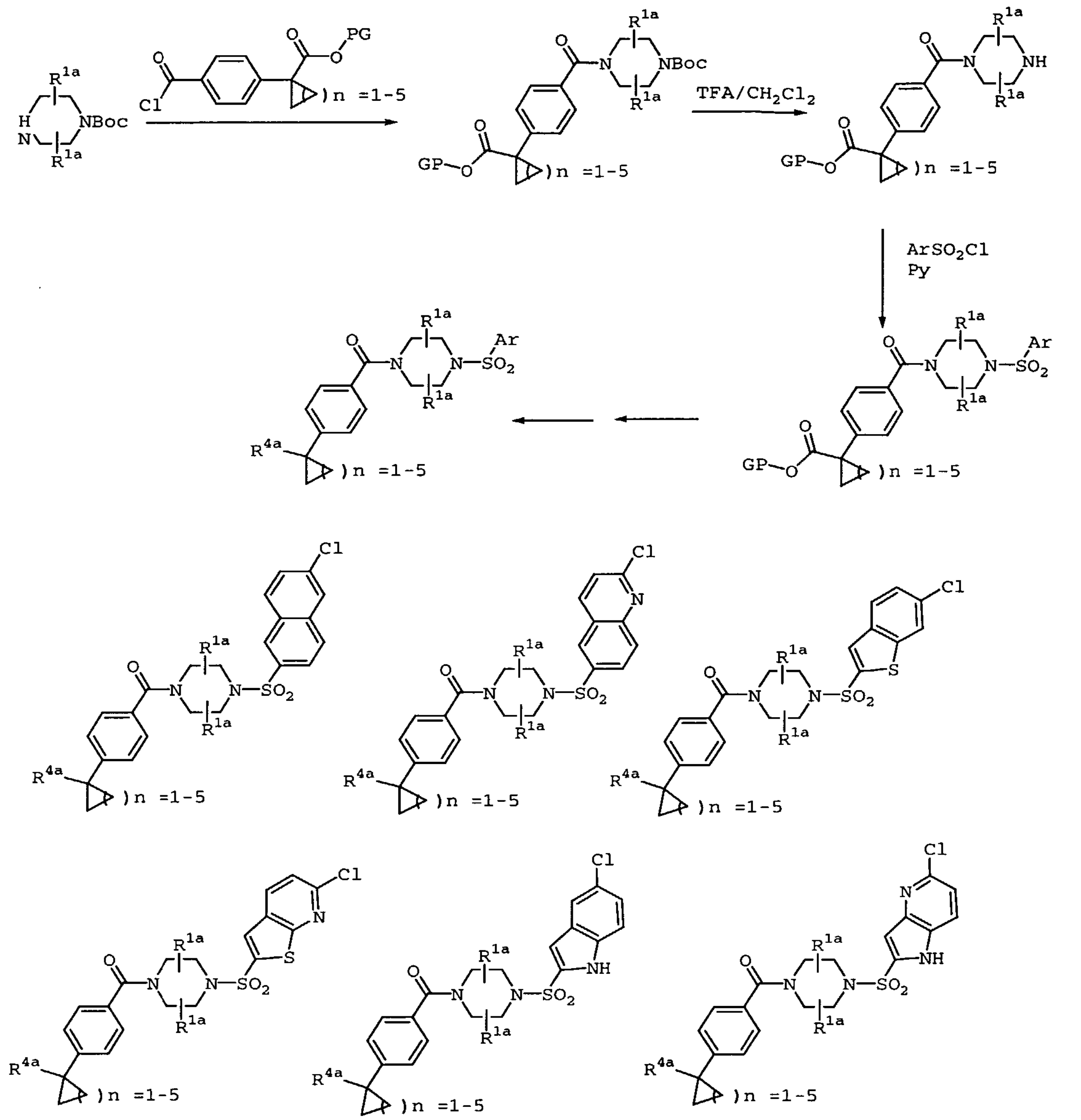
Scheme 32 depicts the synthesis of aminobenzines by using the methods described above and by those skilled in the art.

Scheme 32



Scheme 33 illustrates the synthesis of piperidine derivatives by using the methods described above and known by those skilled in the art.

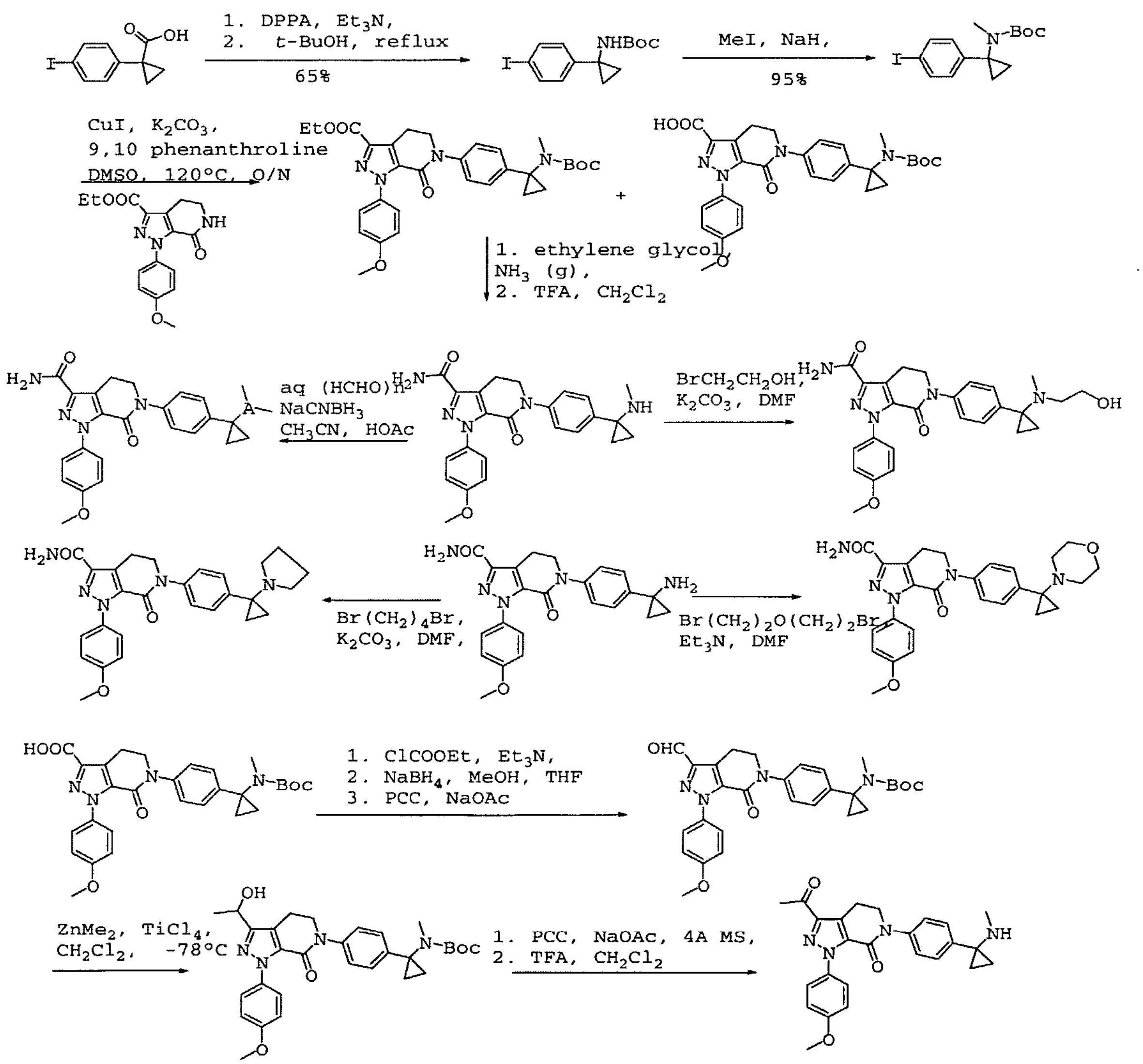
Scheme 33



Scheme 34 depicts the syntheses of phenylcyclopropyl amine derivatives. Starting from 4-iodophenylcyclopropyl carboxylic acid, Curtius rearrangement with DPPA in CH_2Cl_2 at RT followed by heating in *t*-BuOH afforded Boc-protected cyclopropylamine intermediate. This intermediate underwent a sequence of methylation (MeI, NaH, THF), Buchwald Ullman coupling (CuI, K_2CO_3, 9,10-phenanthroline, DMSO), and then amination of the ethyl ester (NH_3 in ethylene glycol) to yield the desire product. Reductive amination with aqueous

formaldehyde and $NaBH_3CN$ in CH_3CN afforded the dimethyl compound. On the other hand, alkylation with bromoethanol dibromobutane, or dibromoethylether using K_2CO_3 as the base yielded tertiary or cyclic amines, respectively. The C3-methylketone analogue was synthesized through a sequence involving a nucleophilic reaction of $ZnMe_2$ with the aldehyde in the presence of $TiCl_4$.

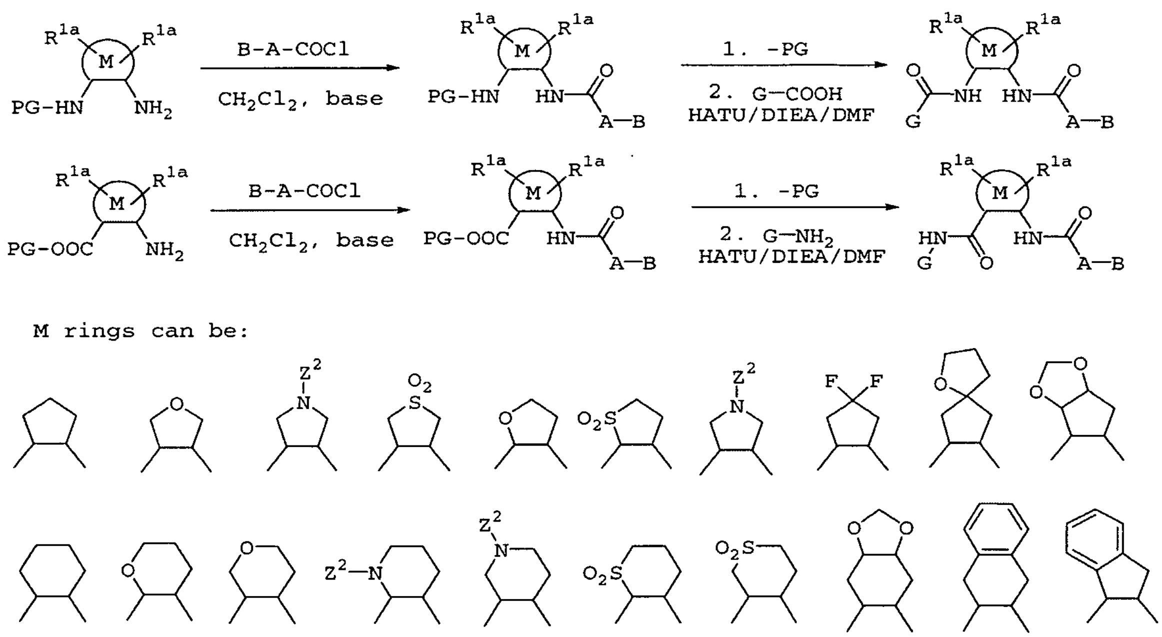
Scheme 34



Compounds of the present invention wherein ring P is absent and ring M is a 3-10 membered non-aromatic carbocycle or heterocycle can also be prepared by using the

methods described previously and known to those skilled in the art. Scheme 34 illustrates a number of nonaromatic M rings that are considered to be part of the present invention. Scheme 34 also describes general methods of converting the shown rings to compounds of the present invention. As one of ordinary skill in the art would recognize, this method would be applicable to other non-aromatic rings not shown.

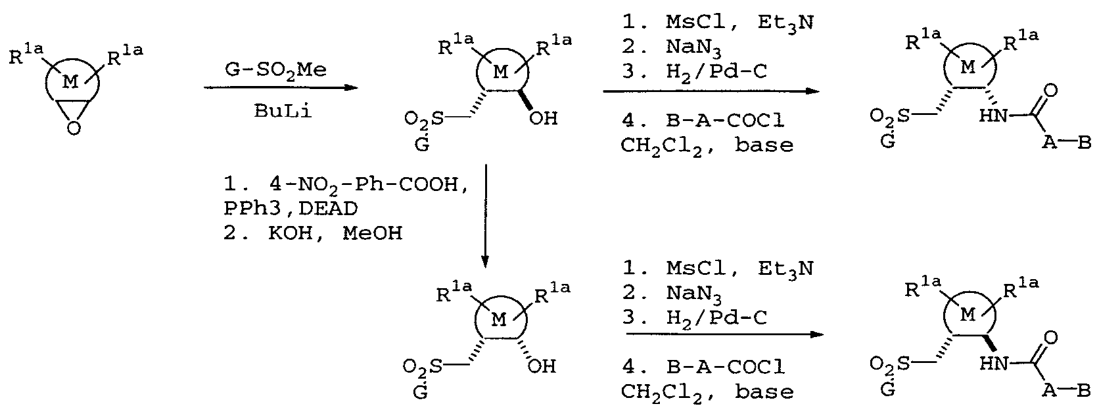
Scheme 35



The properly protected, enantiomerically pure cyclic amino acid cores can be obtained via Davies' protocol (*J. Chem. Soc. Perkin Trans I*, **1994**, 1411) or via the reduction of enamines described by Cimarelli, C. et al (*J. Org. Chem.* **1996**, *61*, 5557). The corresponding diamino compounds can be obtained via saponification of the ester of the cyclic amino acids followed by Curtius rearrangement. On the other hand, the cyclic diamines can be prepared via literature methods. (See, for example, Skarzewski, J. and Gupta, A. *Tetrahedron: Assymmetry*, **1997**, *8*, 1861 and Kim, B. M.; Bae, S. J.; and Seomoon, G., *Tetrahedron Lett.* **1998**, *39*, 6921).

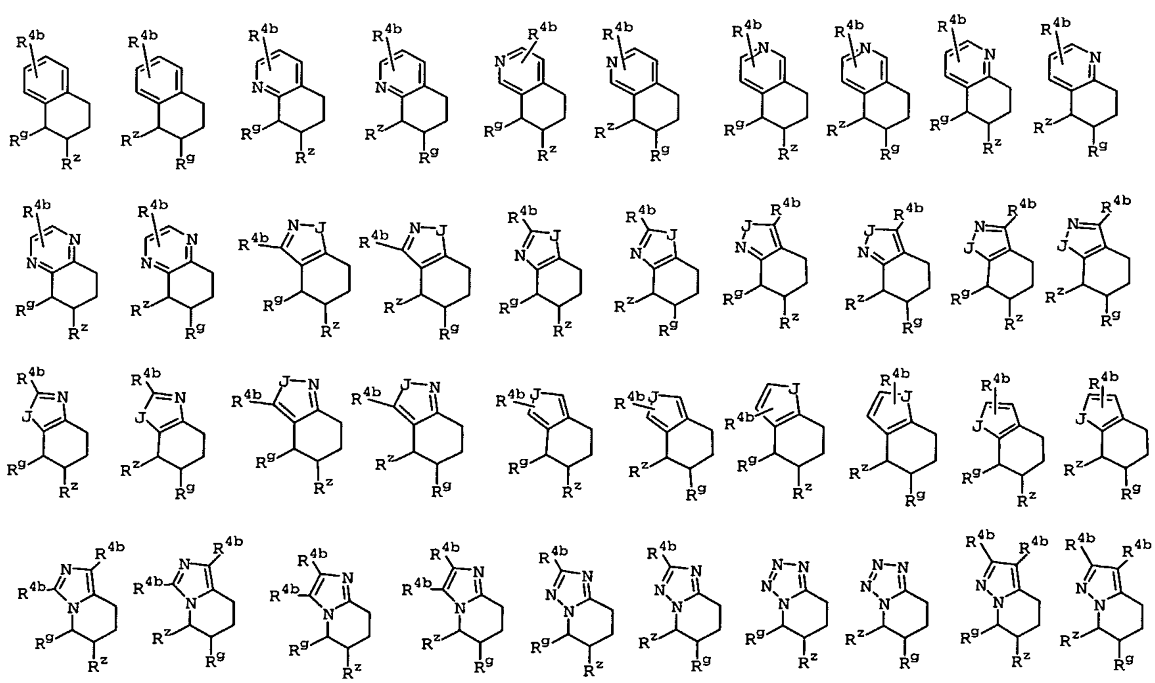
A series of compounds of formula I wherein G_1 is 1,1-dioxo-sulfonylmethyl group are prepared following the sequence outlined in Scheme 36.

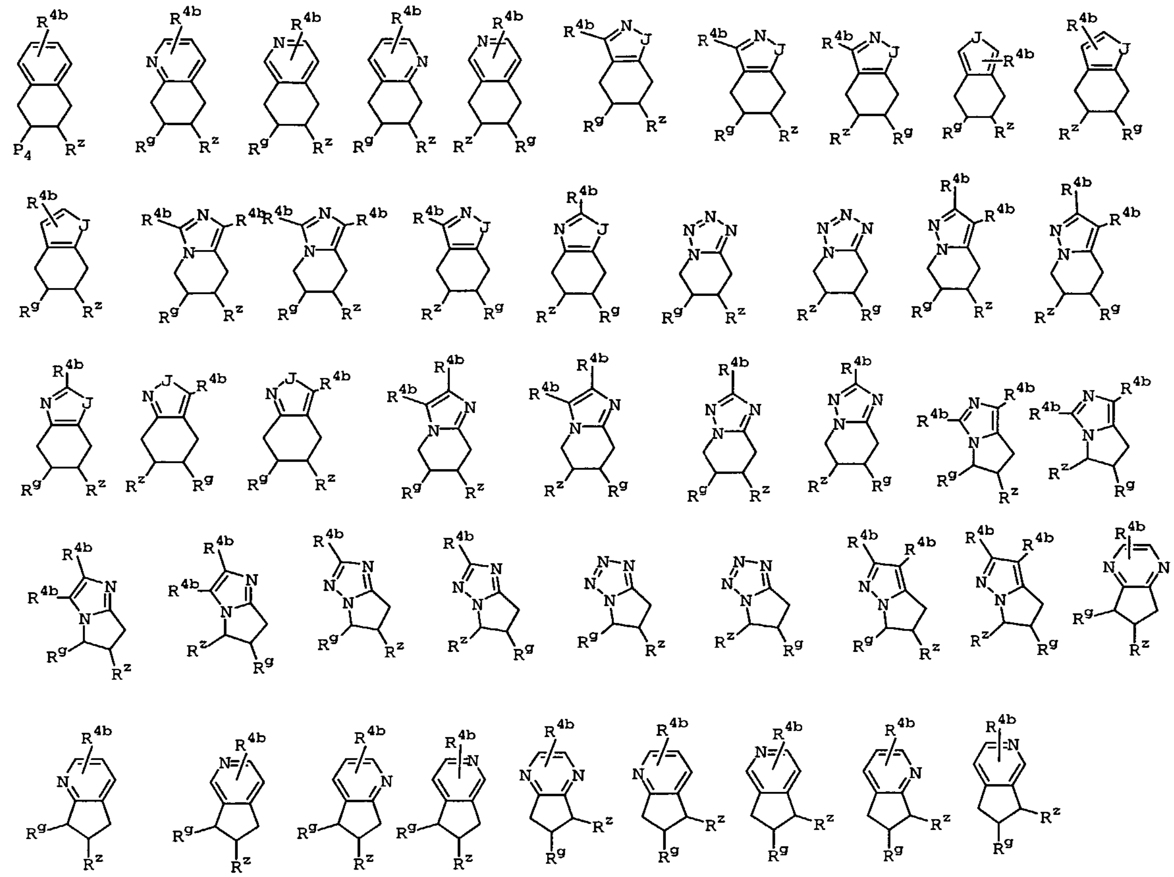
Scheme 36



Scheme 37 illustrates numerous bicyclic M intermediates that can be used to prepare compounds of the present invention. These intermediates can be prepared using methods known to those of ordinary skill in the art and using similar methods described previously.

Scheme 37

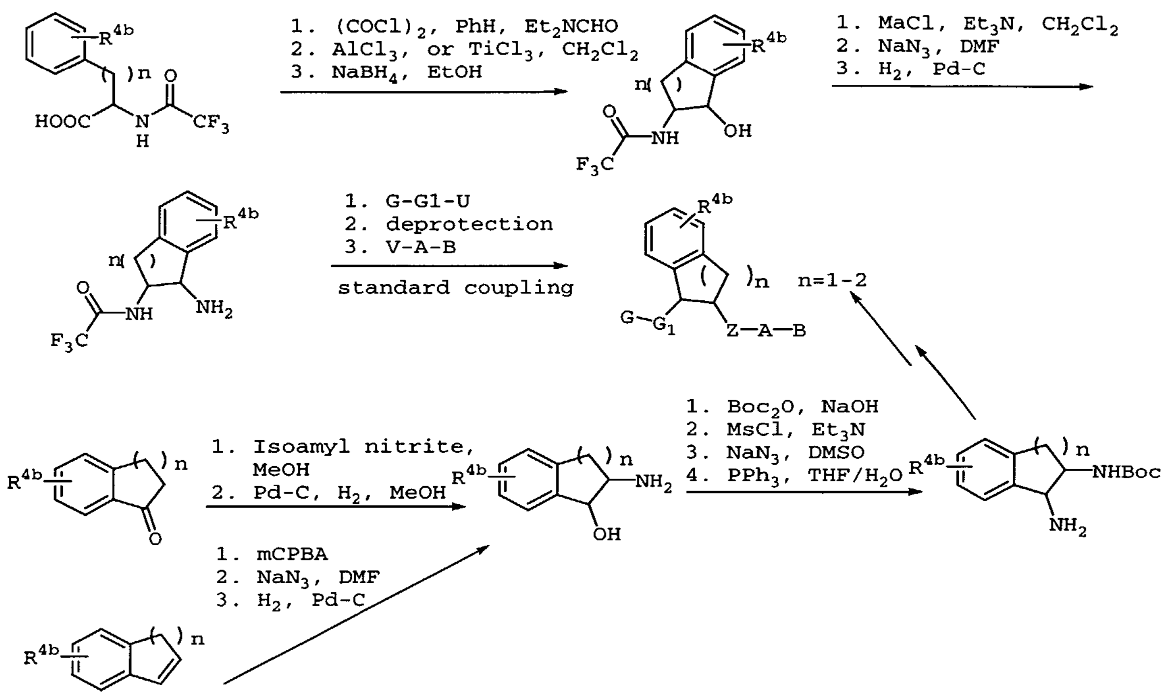




Scheme 38 illustrates the synthesis of benzofused M intermediates of the present invention. The α- or β-amino acid derivatives can undergo Friedel-Crafts reaction followed by reduction to afford the fused ring intermediates. Replacement of the OH group with NH_2 group as described previously, followed by standard coupling reactions will provide the compounds of the present invention. On the other hand, oxime formation of the ketone intermediate followed by reduction with $NaBH_4$ can provide the amino alcohol intermediate, which can also be obtained via epoxidation of the olefin and then nucleophilic displacement. Protection of the amino group followed by azide displacement of the mesylate and then reduction of the azide group will give the Boc protected diamines. Functional groups U and V can be acid chloride, carboxylic acid, sulfonyl chloride, etc. in formula $U\text{-}G_1\text{-}G$

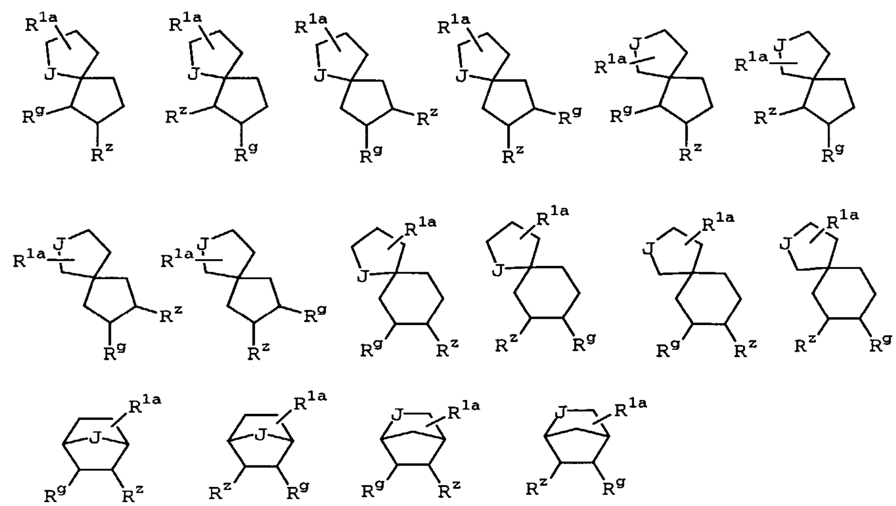
and V-A-B. The compounds of the present invention can be obtained from the mono-Boc protected diamines using methods known to those of ordinary skill in the art and using similar methods described previously.

Scheme 38



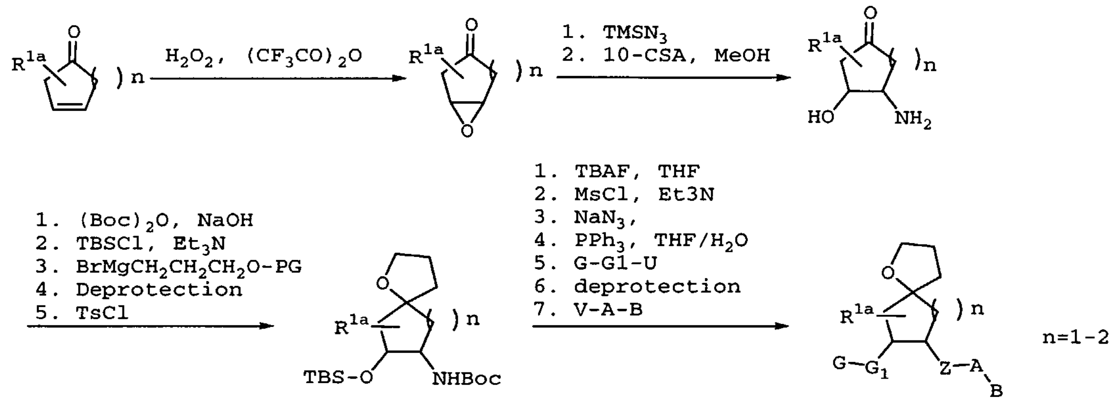
Scheme 39 depicts numerous spiro and bridged M intermediates that can be used to prepare compounds of the present invention. These intermediates can be prepared using methods known to those of ordinary skill in the art and using the methods described previously.

Scheme 39



Scheme 40 depicts the synthesis of spiro intermediates of the present invention. Epoxidation of the olefin followed by displacement with $TMSN_3$ and reduction with 10-CSA can provide the amino alcohol intermediate. Protection of the amino and alcohol groups followed by nucleophilic addition to the carbonyl group and spiro ring formation can afford the spiro tetrahydrafuran intermediate. This intermediate can undergo a similar sequence of reactions described previously to give compounds of the present invention.

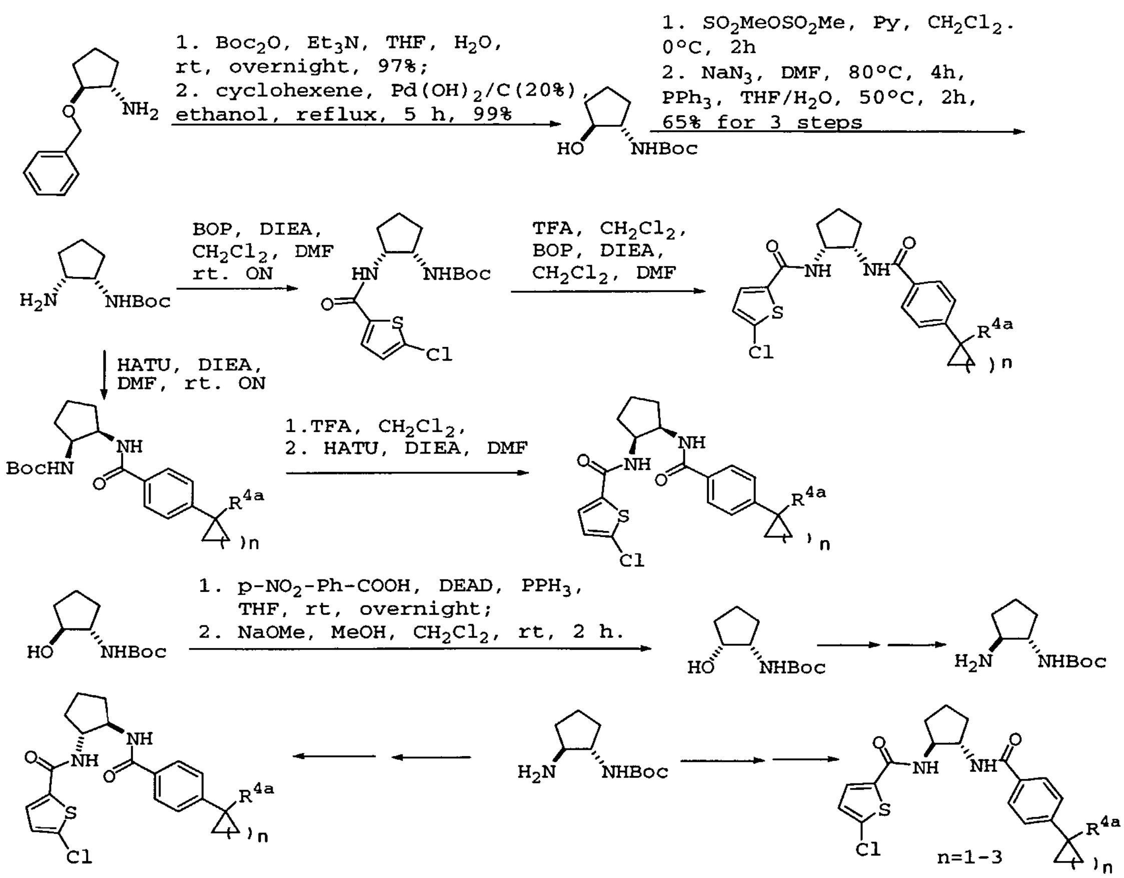
Scheme 40



Different diastereomers of compounds of the present invention can be prepared as exemplified in Scheme 41 with cyclopentyl as the central ring. Starting from

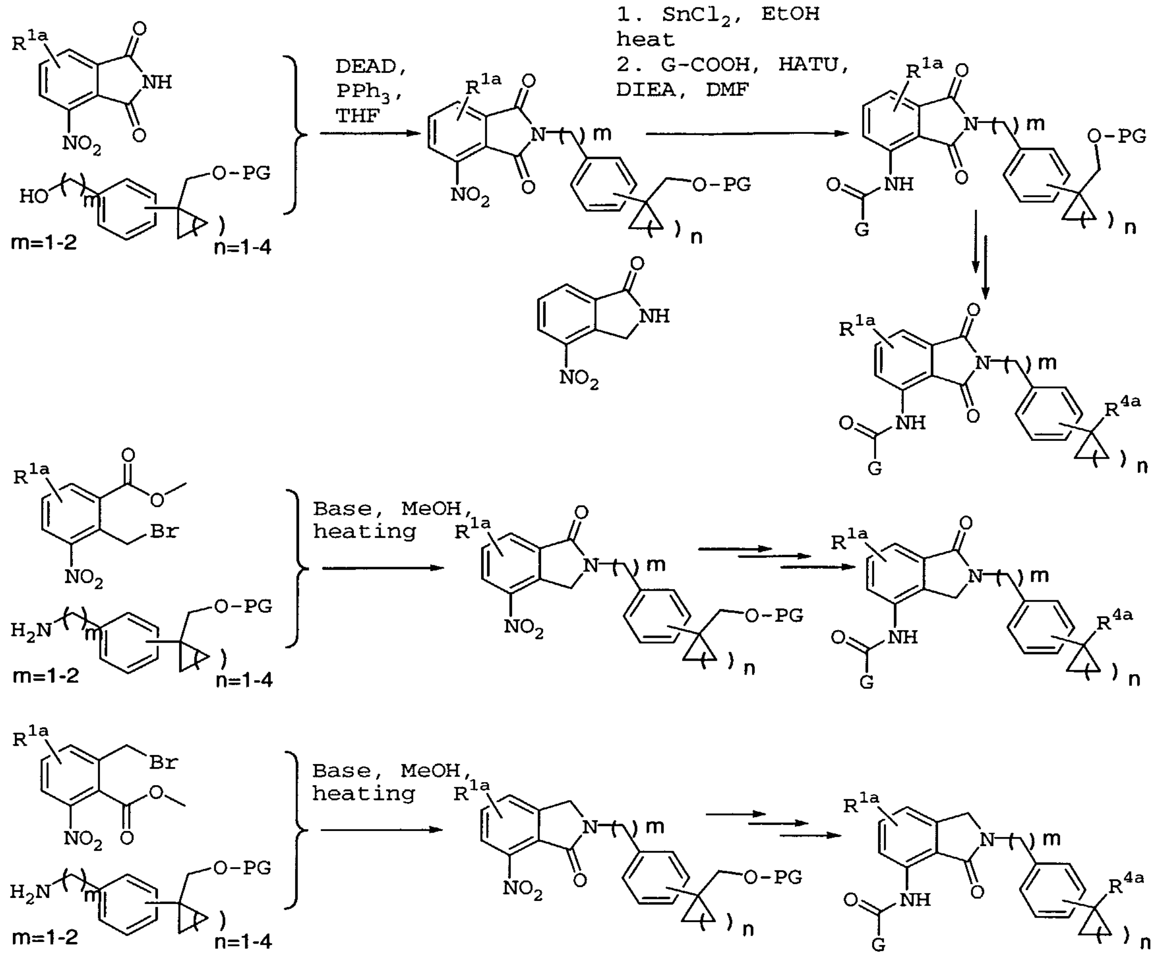
enantiomerically-pure commercially-available (1S, 2S)-2-benzyloxy-cyclopentyl amine, Boc protection followed by debenzylation gave the alcohol. S_N2 displacement with NaN_3 of the mesylate, followed by reduction of the azide afforded the key mono-boc protected diamine intermediate. Amide formation as described previously provided one pair of enantiomers. On the other hand, inversion of the stereo center of the alcohol (p-NO_2-Ph-COOH, DEAD, PPh_3, THF; then NaOMe, MeOH) followed by the same amide formation sequence should afford the other pair of enantiomers.

Scheme 41



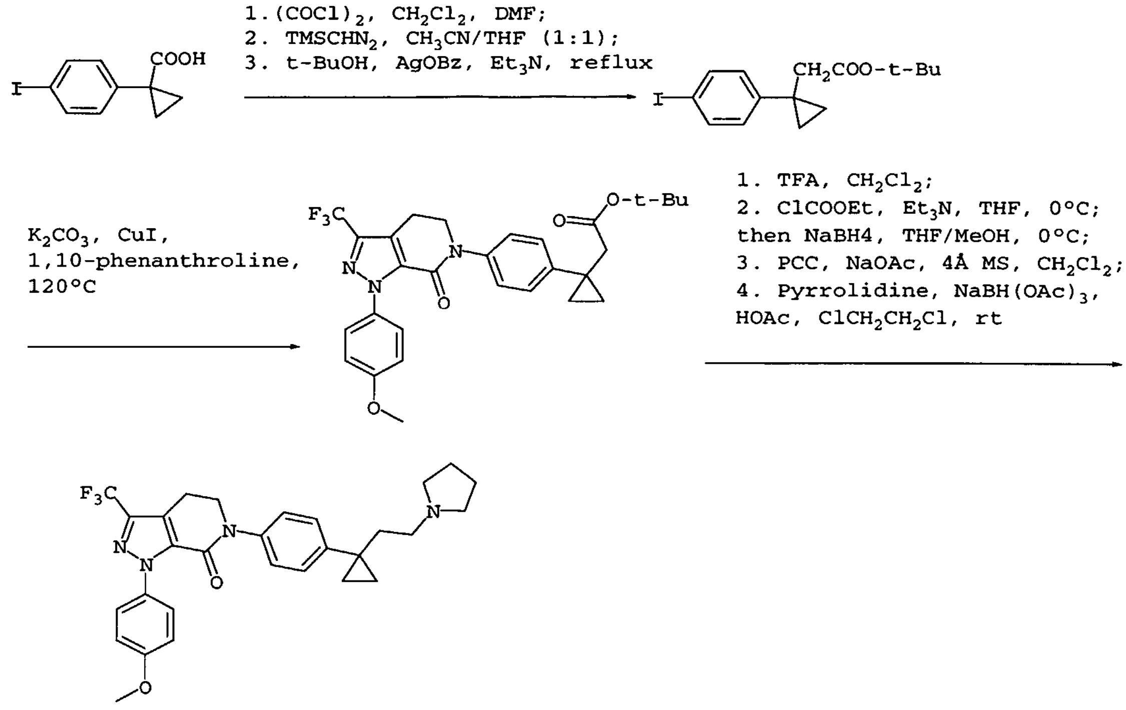
Compounds of present invention wherein M-P is an isoindole derivative can be prepared as exemplified in Scheme 42. These compounds can be obtained via standard organic transformations such as Mitsunomo reactions.

Scheme 42

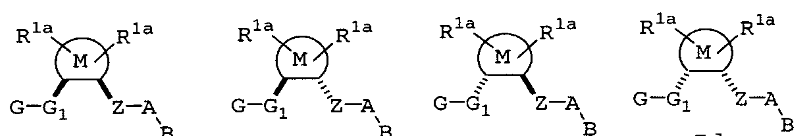


Scheme 43 depict the synthesis of compounds of the present invention wherein R^{4a} is an ethylamine derivative. This synthesis involves homologation of carboxylic acids as the key step.

Scheme 43



One diastereomer of a compound of Formula I may be more potent against fXa than the others. Thus, the following stereochemistries are considered to be a part of the present invention.



Ia Ib Ic Id

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride (Steven D. Young, et al, *Antimicrobial Agents and Chemotheraphy*, **1995**, 2602-2605). A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand (for example, Andrew S. Thompson, et al, *Tetrahedron Lett.* **1995**, *36*, 8937-8940).

Other features of the invention will become apparent in the course of the following descriptions of exemplary

embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

UTILITY

The compounds of this invention are inhibitors of factor Xa and are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals (i.e., factor Xa-associated disorders). In general, a thromboembolic disorder is a circulatory disease caused by blood clots (i.e., diseases involving fibrin formation, platelet activation, and/or platelet aggregation). The term "thromboembolic disorders" as used herein includes arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart. The term "thromboembolic disorders" as used herein also includes specific disorders selected from, but not limited to, unstable angina or other acute coronary syndromes, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a) prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis. It is noted that thrombosis includes occlusion (e.g. after a bypass) and reocclusion (e.g., during or after percutaneous transluminal coronary angioplasty). The thromboembolic disorders may result from conditions including but not limited to atherosclerosis, surgery or surgical complications, prolonged immobilization, arterial fibrillation, congenital thrombophilia, cancer, diabetes,

effects of medications or hormones, and complications of pregnancy. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Diapharma/Chromogenix, West Chester, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nM. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i.

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5% PEG 8000. The Michaelis constant, K_m, for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o-v_s)/v_s = I/(K_i\ (1+ S/K_m))$$

where:

v_o is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

Compounds tested in the above assay are considered to be active if they exhibit a K_i of ≤ 10 μM. Preferred compounds of the present invention have K_i's of ≤ 1 μM. More preferred compounds of the present invention have K_i's of ≤ 0.1 μM. Even more preferred compounds of the present invention have K_i's of ≤ 0.01 μM. Still more preferred compounds of the present invention have K_i's of ≤ 0.001 μM. Using the methodology described above, a number of compounds of the present invention were found to exhibit K_i's of ≤ 10 μM, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing that contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group. The ID_{50} values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of the present invention may also be useful as inhibitors of serine proteases, notably human thrombin, Factor VIIa, Factor IXa, Factor XIa, urokinase, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm that arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described

above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μm, thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of the present invention that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that a compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin (either unfractionated heparin or any commercially available low molecular weight heparin), synthetic pentasaccharide, direct acting thrombin inhibitors including hirudin and argatrobanas well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function, for example by inhibiting the aggregation, adhesion or granular secretion of platelets. Agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, and pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA) and piroxicam are preferred. Other suitable platelet inhibitory agents include IIb/IIIa antagonists (e.g., tirofiban, eptifibatide, and abciximab), thromboxane-A2-receptor antagonists (e.g., ifetroban), thromboxane-A2-synthetase inhibitors, PDE-III inhibitors (e.g., dipyridamole), and pharmaceutically acceptable salts or prodrugs thereof.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, is also intended to include ADP (adenosine diphosphate) receptor antagonists, preferably antagonists of the purinergic receptors P_2Y_1 and P_2Y_{12}, with P_2Y_{12} being even more preferred. Preferred P_2Y_{12} receptor antagonists include ticlopidine and clopidogrel, including pharmaceutically acceptable salts or prodrugs thereof. Clopidogrel is an even more preferred agent. Ticlopidine and clopidogrel are also preferred compounds since they are known to be gentle on the gastro-intestinal tract in use.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors

are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boropeptides, heparins, hirudin, argatroban, and melagatran, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

The term thrombolytics or fibrinolytic agents (or thrombolytics or fibrinolytics), as used herein, denote agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator (natural or recombinant) and modified forms thereof, anistreplase, urokinase, streptokinase, tenecteplase (TNK), lanoteplase (nPA), factor VIIa inhibitors, PAI-1 inhibitors (i.e., inactivators of tissue plasminogen activator inhibitors), alpha2-antiplasmin inhibitors, and anisoylated plasminogen streptokinase activator complex, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in EP 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Examples of suitable anti-arrythmic agents for use in combination with the present compounds include: Class I agents (such as propafenone); Class II agents (such as carvadiol and propranolol); Class III agents (such as sotalol, dofetilide, amiodarone, azimilide and ibutilide); Class IV agents (such as ditiazem and verapamil); K^+

channel openers such as I_{Ach} inhibitors, and I_{Kur} inhibitors (e.g., compounds such as those disclosed in WO01/40231).

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include: alpha adrenergic blockers; beta adrenergic blockers; calcium channel blockers (e.g., diltiazem, verapamil, nifedipine, amlodipine and mybefradil); diruetics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone); renin inhibitors; ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril); AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan); ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265); Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389); neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat, gemopatrilat and nitrates).

Examples of suitable calcium channel blockers (L-type or T-type) for use in combination with the compounds of the present invention include diltiazem, verapamil, nifedipine, amlodipine and mybefradil.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable diruetics for use in combination with the compounds of the present invention include: chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone,

furosemide, musolimine, bumetanide, triamtrenene, amiloride, and spironolactone.

Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include sprionolactone and eplirinone.

Examples of suitable phospodiesterase inhibitors for use in combination with the compounds of the present invention include: PDE III inhibitors (such as cilostazol); and PDE V inhibitors (such as sildenafil).

Examples of suitable cholesterol/lipid lowering agents and lipid profile therapies for use in combination with the compounds of the present invention include: HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, fluvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or atavastatin or visastatin)); squalene synthetase inhibitors; fibrates; bile acid sequestrants (such as questran); ACAT inhibitors; MTP inhibitors; lipooxygenase inhibitors; choesterol absorption inhibitors; and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include: biguanides (e.g., metformin); glucosidase inhibitors (e.g., acarbose); insulins (including insulin secretagogues or insulin sensitizers); meglitinides (e.g., repaglinide); sulfonylureas (e.g., glimepiride, glyburide and glipizide); biguanide/glyburide combinations (e.g., glucovance), thiozolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in WO00/59506, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-depressant agents for use in combination with the compounds of the present invention include nefazodone and sertraline.

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include: prednisone; dexamethasone; enbrel; protien tyrosine kinase (PTK) inhibitors; cyclooxygenase inhibitors (including NSAIDs, and COX-1 and/or COX-2 inhibitors); aspirin; indomethacin; ibuprofen; prioxicam; naproxen; celecoxib; and/or rofecoxib.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate and raloxifene.

Examples of suitable hormone replacement therapies for use in combination with the compounds of the present invention include estrogen (e.g., congugated estrogens) and estradiol.

Examples of suitable anti-coagulants for use in combination with the compounds of the present invention include heparins (e.g., unfractioned and low molecular weight heparins such as enoxaparin and dalteparin).

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include orlistat and aP2 inhibitors (such as those disclosed in WO00/59506).

Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, and hydroxyzine pamoate.

Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, adriamycin; epithilones, cisplatin, and carboplatin.

Examples of suitable anti-ulcer and gastroesophageal reflux disease agents for use in combination with the

compounds of the present invention include famotidine, ranitidine, and omeprazole.

Administration of the compounds of the present invention (i.e., a first therapeutic agent) in combination with at least one additional therapeutic agent (i.e., a second therapeutic agent), preferably affords an efficacy advantage over the compounds and agents alone, preferably while permitting the use of lower doses of each (i.e., a synergistic combination). A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety. It is preferred that at least one of the therapeutic agents is administered in a sub-therapeutic dose. It is even more preferred that all of the therapeutic agents be administered in sub-therapeutic doses. Sub-therapeutic is intended to mean an amount of a therapeutic agent that by itself does not give the desired therapeutic effect for the condition or disease being treated. Synergistic combination is intended to mean that the observed effect of the combination is greater than the sum of the individual agents administered alone.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of a thromboembolic disorder (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent to treat a thromboembolic disorder. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle,

jar, vial, flask, syringe, tube (e.g., for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (e.g., cardboard or plastic), crates, cartons, bags (e.g., paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (e.g., the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (e.g., paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (e.g., printed or applied).

Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl callulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the

atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl-or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing

100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P, and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of the present invention are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent,

preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but ratheR is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical

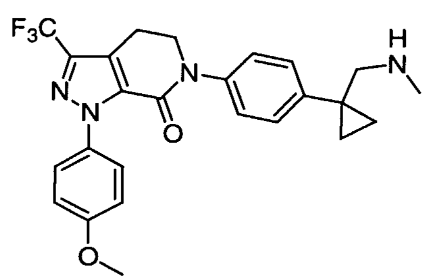
contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low-viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are afforded for illustration of the invention and are not intended to be limiting thereof.

Example 1

1-(4-methoxyphenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Part A. δ-Valerolactam (22.22 g, 222.89 mmol) was stirred in $CHCl_3$ (500 mL) at 0°C. PCl_5 (140.0 g, 68.29 mmol) was added portionwise. The resulting slurry was stirred at reflux for 3 h until the solution became clear. The mixture was cooled in an ice bath and H_2O was added carefully until the PCl_5 was quenched completely. The two layers were separated. The organic layer was washed with H_2O (3x) and brine (2x), dried over $MgSO_4$, filtered, and concentrated to dryness to give 3,3-dichloro-2-piperidinone (31.63 g, yield: 85%). This solid (16.50 g, 98.80 mmol) was dissolved in DMF (20 mL), and Li_2CO_3 (21.93 g, 296.40 mmol, 3.0 eq) was added. The mixture was stirred at 120°C for 1 day. The solvent was further concentrated, and 1N HCl was added to acidify the mixture. It was then extracted with $CHCl_3$ (6x). The organic layers were washed with H_2O, brine, dried over $MgSO_4$, and concentrated to dryness to give almost pure 3-chloro-5,6-dihydro-2(1*H*)-pyridinone (11.13 g, 87%).

Part B. The product from Part A (5.50 g, 41.98 mmol) and 2,2,2-trifluoro-N-(4-methoxyphenyl)-ethanehydrazonoyl bromide (12.90 g, 43.58 mmol) were stirred in toluene (100 mL) at room temperature under N_2. Et_3N (28.0 mL, 200.1 mmol) was then added. The mixture was stirred at 85°C for 15 h. It was cooled to room temperature and extracted with EtOAc (3x). The organic layers were washed with H_2O (2x) and brine (2x), dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2, then CH_2Cl_2:EtOAc=4:1, then EtOAc) to produce 1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one as a light-tan solid (5.09 g, yield: 39%). LC/MS (ESI^+) 312.4 $(M+H)^+$.

Part C. 1-Phenyl-cyclopropylcarboxylic acid (16.50 g, 101.0 mmol) was stirred in HOAc (70 mL) at RT under N_2. I_2 (27.94 g, 101.0 mmol) was added, followed by the addition of $NaIO_3$ (4.98 g, 25.25 mmol) and conc. H_2SO_4 (1 mL). The resulting mixture was stirred at 70°C for 3 days. LC-MS showed completion of the reaction. The cooled mixture was concentrated, poured into H_2O, and extracted with EtOAc (2x). The organic layer was washed with sodium thiosulfate (2x) and brine, dried over $MgSO_4$, filtered, and concentrated to dryness to give almost pure 4-iodophenylcyclopropyl carboxylic acid (23.56 g, yield: 81%). LC/MS (ESI^+) 472.4 $(M+H)^+$.

Part D. The product of part C (0.22 g, 0.76 mmol) and the product from part B (0.11 g, 0.35 mmol) were stirred in DMSO (0.5 mL) under N_2. K_2CO_3 (0.15 g, 1.09 mmol, 3.0 eq) was added, followed by the addition of 1,10-phenanthroline (28 mg, 20mol%) and CuI (30 mg, 20%mol). The resulting mixture was stirred at 130°C overnight. LC-MS showed completion of the reaction. EtOAc was added to the cooled solution. It was washed with 1N HCl, H_2O, and brine; dried over $MgSO_4$; filtered; and concentrated in *vacuo* to give almost pure 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl] phenyl}cyclopropanecarboxylic acid (460 mg, 94%). LC/MS (ESI^+) 472.6 $(M+H)^+$, t_R = 2.39 min (35-98% CH_3CN in H_2O in a 6-min run).

Part E. The product from Part D (0.28 g, 0.59 mmol) was stirred in THF (5 mL) at 0°C under N_2. Et_3N (0.15 mL, 1.06 mmol) was added, followed by dropwise addition of $ClCO_2Et$ (0.098 mL, 1.03 mmol). The reaction mixture was then stirred at 0°C for 1 h. TLC showed the completion of the reaction. The mixture was filtered through a filter funnel

and rinsed with anhydrous THF. The THF filtrate (ca. 10 mL) was stirred at 0°C under N_2. MeOH (2.5 mL) was added followed by addition of $NaBH_4$ (0.31 g, 8.16 mmol, 13.8 eq) portionwise. The resulting mixture was stirred at 0°C for 15 min. Analytical LC-MS showed completion of the reaction. Sat'd Na_2SO_4 was then added. The mixture was extracted with EtOAc (2x). The organic layer was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give 6-{4-[1-(hydroxymethyl)cyclopropyl]phenyl}-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (0.23 g, 84.7%). LC/MS(ESI$^+$) 458.6 $(M+H)^+$, t_R = 6.06 min (5-98% CH_3CN in H_2O in a 10-min run). ^1H NMR ($CHCl_3$) δ 7.38 (d, J = 9.1 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.16 (m, 2H), 6.83 (d, J = 9.1 Hz, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.72 (s, 3H), 3.54 (s, 2H), 3.07 (t, J = 6.6 Hz, 2H), 0.75 (s, br, 2H) ppm.

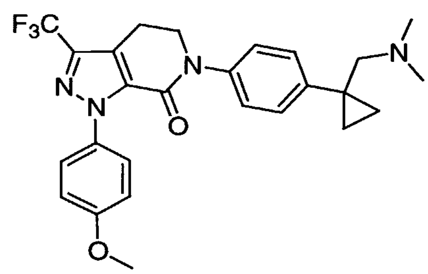
The above aldehyde (0.22 g, 0.49 mmol) was stirred in anhydrous CH_2Cl_2 (5 mL) at RT under N_2. NaOAc (88 mg, 1.07 mmol, 2.2 eq) and 4Å molecular sieves (200 mg) were added, followed by the addition of PCC (0.19 g, 0.88 mmol, 1.8 eq). The resulting slurry was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was filtered through Celite® and rinsed with CH_2Cl_2. The filtrate was washed with H_2O (2x) and brine (2x), dried over Na_2SO_4, filtered, and concentrated to dryness to give almost pure 1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}cyclopropanecarbaldehyde (0.20 g, yield: 87.4%). LC/MS (ESI$^+$) 455.4 $(M+H)^+$.

Part F. The product from Part E (20 mg, 0.95 mmol), methylamine hydrochloride (20 mg, excess) were stirred in

dichloroethane (0.7 mL) in a capped vial. $NaBH(OAc)_3$ (50 mg, excess) was added, followed by addition of one drop of HOAc. The reaction mixture was stirred at RT for 1.5 h. Analytical LC-MS showed completion of the reaction. The mixture was evaporated, and dissolved in aqueous MeOH. It was then purified by prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run, t_R = 4.65 min) to obtain the product 1-(4-methoxy-phenyl)-6-(4-{1-[(methylamino)methyl]cyclopropyl}phenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (18 mg, 86%). LC/MS (ESI$^+$) 471.4 $(M+H)^+$. HRMS $C_{25}H_{26}O_2F_3N_4$ $(M+H)^+$ 471.2011 calcd for 471.2008. ^1H NMR (acetone-d_6) δ 7.51 (m, 4H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.99 (d, *J* = 9.1 Hz, 2H), 4.16 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.37 (m, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 2.70 (s, 3H), 1.27 (d, *J* = 6.2 Hz, 6H), 1.12 (m, 2H), 0.96 (m, 2H) ppm.

Example 2

6-(4-{1-[(dimethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

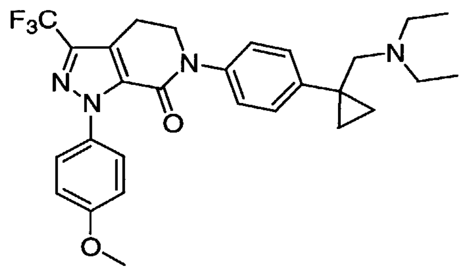


Following a procedure analogous to that used for step F in Example 1, but using dimethylamine hydrochloride, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 485.4 $(M+H)^+$, t_R = 4.66 min. HRMS $C_{26}H_{28}O_2F_3N_4$ $(M+H)^+$ 485.2158 calcd for 485.2164. ^1H NMR (acetone-d_6) δ 7.51 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.60 (m, 2H), 3.16 (t, *J*

= 6.3 Hz, 2H), 2.82 (s, 6H), 1.15 (m, 2H), 1.08 (m, 2H) ppm.

Example 3

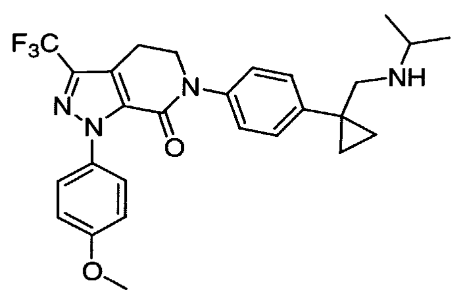
6-(4-{1-[(diethylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for step F in Example 1, but using diethylamine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 513.4 $(M+H)^+$, t_R = 4.79 min.

Example 4

6-(4-{1-[(isopropylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

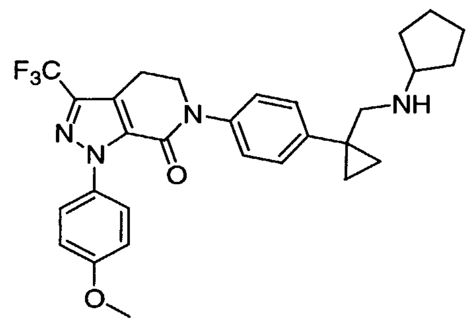


Following a procedure analogous to that used for step F in Example 1, but using isopropylamine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI^+) 499.4 $(M+H)^+$, t_R = 4.79 min. ^1H NMR (acetone-d_6) δ 7.51 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.1 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.16

(t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.45 (m, 1H), 3.37 (m, 2H), 3.16 (t, J = 6.3 Hz, 2H), 1.27 (d, J = 6.2 Hz, 6H), 1.13 (m, 2H), 0.93 (m, 2H) ppm.

Example 5

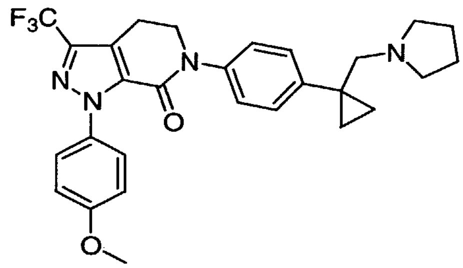
6-(4-{1-[(cyclopentylamino)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for step F in Example 1, but using cyclopentylamine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS (ESI$^+$) 525.4 $(M+H)^+$, t_R = 5.03 min. HRMS $C_{29}H_{32}O_2F_3N_4$ $(M+H)^+$ 525.2486 calcd for 525.2477. ^1H NMR (acetone-d_6) δ 7.50 (m, 4H), 7.31 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.62 (m, 1H), 3.31 (m, 2H), 3.16 (t, J = 6.5 Hz, 2H), 1.99 (m, 2H), 1.68 (m, 4H), 1.50 (m, 2H), 1.14 (m, 2H), 0.96 (m, 2H) ppm.

Example 6

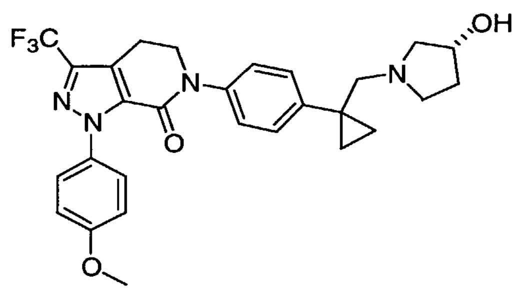
1-(4-methoxyphenyl)-6-{4-[1-(1-pyrrolidinylmethyl)cyclopropyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for step F in Example 1, but using pyrrolidine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 511.4 $(M+H)^+$, t_R = 4.86 min. HRMS $C_{28}H_{30}O_2F_3N_4$ $(M+H)^+$ 511.2320 calcd for 511.2321. ^{1}H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.17 (t, *J* = 6.6 Hz, 2H), 3.83 (s, 3H), 3.60 (m, 2H), 3.49 (m, 2H), 3.16 (t, *J* = 6.3 Hz, 2H), 2.93 (m, 2H), 1.93 (m, 4H), 1.14 (m, 2H), 1.01 (m, 2H) ppm.

Example 7

6-[4-(1-{[(3*R*)-3-hydroxy-1-pyrrolidinyl]methyl}cyclopropyl)phenyl]-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt

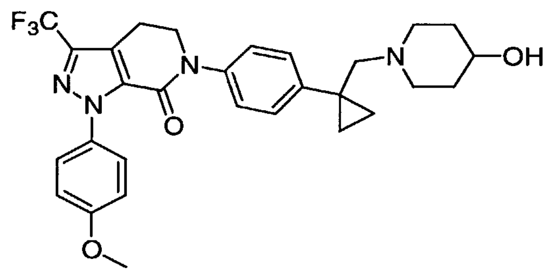


Following a procedure analogous to that used for step F in Example 1, but using (*R*)-(+)-pyrrolidinol, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 527.4 $(M+H)^+$, t_R = 4.49 min. ^{1}H NMR (acetone-d_6) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 9.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz,

2H), 6.98 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.72 (m, 1H), 3.40-3.27 (m, 4H), 3.16 (t, J = 6.3 Hz, 2H), 1.92 (m, 2H), 1.15 (m, 2H), 1.02 (m, 2H) ppm.

Example 8

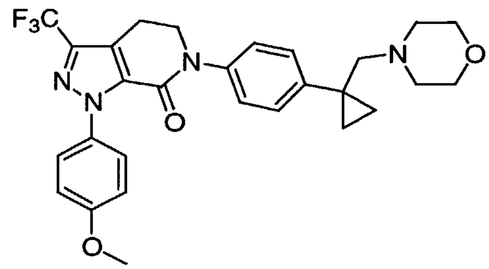
6-(4-{1-[(4-hydroxy-1-piperidinyl)methyl]cyclopropyl}phenyl)-1-(4-methoxyphenyl)-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for step F in Example 1, but using 4-hydroxypiperidine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 541.4 $(M+H)^+$, t_R = 4.63 min. ^1H NMR (acetone-d_6) δ 7.51 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.5 Hz, 2H), 3.83 (s, 3H), 3.58 (m, 2H), 3.38 (m, 5H), 3.16 (t, J = 6.3 Hz, 2H), 1.92 (m, 2H), 1.78 (m, 2H), 1.19 (m, 2H), 1.05 (m, 2H) ppm.

Example 9

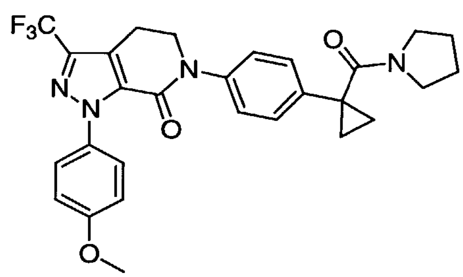
1-(4-methoxyphenyl)-6-{4-[1-(4-morpholinylmethyl)cyclopropyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one, trifluoroacetic acid salt



Following a procedure analogous to that used for step F in Example 1, but using morpholine, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 527.4 $(M+H)^+$, t_R = 6.08 min. HRMS $C_{28}H_{30}O_3F_3N_4$ $(M+H)^+$ 527.2280 calcd for 527.2270. ^1H NMR (acetone-d_6) δ 7.52 (m, 4H), 7.33 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 9.1 Hz, 2H), 4.17 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.64 (m, 1H), 3.17 (t, J = 6.6 Hz, 2H), 1.92 (m, 2H), 1.18 (t, J = 4.4 Hz, 2H), 1.06 (t, J = 4.4 Hz, 2H) ppm.

Example 10

1-(4-methoxyphenyl)-6-{4-[1-(1-pyrrolidinylcarbonyl)cyclopropyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one

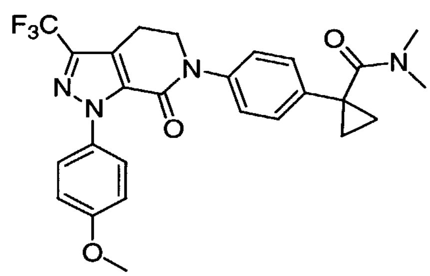


Part A. The product from part D of Example 1 (0.21 g, 0.45 mmol) was stirred in CH_2Cl_2 (10 mL) at RT under N_2. $SOCl_2$ (0.1 mL) was added. The mixture was stirred at RT for 1 h. It was then concentrated to dryness in *vacuo*. The product (20 mg) was stirred in CH_2Cl_2 (0.6 mL). Pyrrolidine (0.02 mL) was added, followed by the addition of DIEA (0.05 mL) and one piece of DMAP. The mixture was stirred at RT for

0.5 h. LC-MS showed completion of the reaction. It was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run) to afford 1-(4-methoxyphenyl)-6-{4-[1-(1-pyrrolidinyl carbonyl)cyclopropyl]phenyl}-3-(trifluoromethyl)-1,4,5,6-tetrahydro-7*H*-pyrazolo[3,4-*c*]pyridin-7-one (15 mg, yield, 67%). LC/MS(ESI$^+$) 525.4 $(M+H)^+$, t_R = 6.17 min. ^1H NMR (acetone-d_6) δ 7.49 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.97 (d, J = 9.1 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.35 (m, 2H), 3.20 (m, 2H), 3.16 (t, J = 6.6 Hz, 2H), 1.74 (m, 4H), 1.31 (m, 2H), 1.08 (m, 2H) ppm.

Example 11

1-{4-[1-(4-methoxyphenyl)-7-oxo-3-(trifluoromethyl)-1,4,5,7-tetrahydro-6*H*-pyrazolo[3,4-*c*]pyridin-6-yl]phenyl}-*N*,*N*-dimethylcyclopropanecarboxamide



Following a procedure analogous to that used for the preparation of Example 10, but using dimethylamine hydrochloride, the title compound was prepared. The product was purified by RP-prep LC-MS (5-98% CH_3CN/H_2O in a 10-min run). LC/MS(ESI$^+$) 499.4 $(M+H)^+$, t_R = 6.01 min. HRMS $C_{26}H_{26}O_3F_3N_4$ $(M+H)^+$ 499.1948 calcd for 499.1957. ^1H NMR (acetone-d_6) δ 7.49 (d, J = 9.1 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.16 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.16 (t, J = 6.2 Hz, 2H), 2.87 (s, 6H), 1.30 (m, 2H), 1.14 (m, 2H) ppm.

Example 12